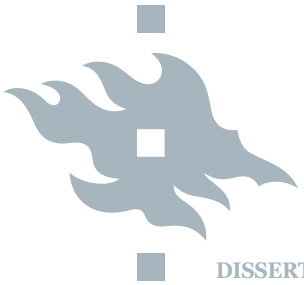

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Health-Related Quality of Life and Cost-Utility in Bulimia Nervosa and Anorexia Nervosa in Women

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HEALTH-RELATED QUALITY OF LIFE AND COST-UTILITY IN BULIMIA NERVOSA AND ANOREXIA NERVOSA IN WOMEN

Veera Pohjolainen

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To Antti, Pirkka and Eero

ABSTRACT

Pohjolainen Veera. Health-related quality of life and cost-utility in bulimia nervosa and anorexia nervosa in women.

Eating disorders (ED) are serious medical conditions leading to high mortality and having a major impact on the health-related quality of life (HRQoL) of the sufferers. HRQoL is the most commonly used measure of the quality of life subconcept, assessing one's life specifically in relation to health. In addition, the costs of treating EDs are considered high. Despite these facts, the cost-effectiveness of treatment in terms of quality-adjusted life years (QALYs) (i.e. cost-utility) has not previously been studied. There is no information on the long-term quality of life in eating disorders, and the prognostic factors regarding HRQoL are undetermined.

The aims of this naturalistic follow-up study were to measure the cost-utility (i.e. the cost per QALY) of the treatment of bulimia nervosa (BN) (Study I) and anorexia nervosa (AN) (Study II), to identify prognostic factors related to HRQoL in AN using the Bayesian method (Study III) and to measure the long-term development of HRQoL in AN and BN (Study IV). The study participants comprised 72 AN (mean age 23 SD 7.3) and 110 BN (mean age 25 SD 6.3) patients, who were mainly young females, entering treatment in the Eating Disorder Unit of Helsinki University Central Hospital, Finland, from June 2002 to December 2003. The Eating Disorder Unit provides treatment at the tertiary care level for adult ED patients within a catchment area of approximately 1.5 million people. Most treatment is provided at the outpatient level, but day patient treatment and inpatient wards are also available. The patients were asked to complete the 15D HRQoL questionnaire and the Eating Disorder Inventory (EDI) questionnaire, as well as a specific questionnaire developed for the needs of this study before the start of treatment. Follow-up questionnaires were mailed at 6 months, 2 years and approximately 8 years after the beginning of the treatment. All patients received normal hospital treatment and were followed up in a naturalistic setting in order to gain more information on the everyday-life effectiveness of ED treatment. Direct hospital costs concerning the treatment of individual patients in the Eating Disorder Unit were obtained from the clinical patient administration system (Ecomed®).

The quality-adjusted life years (QALYs) gained were calculated and the cost-utility was assessed. Two assumptions based on the development of HRQoL in eating disorders were made: the best-case scenario (i.e. the most optimistic scenario) and the base-case scenario (i.e. the most pessimistic scenario). Prognostic factors concerning AN were investigated based on a

Bayesian approach, which allows the analysis of small data sets, and was performed using a naïve Bayes classifier.

The baseline HRQoL of BN and AN patients was poor, but improved during the follow-up (6 months in BN, 2 years in AN). The cost per QALY in BN varied from €1455 (best-case scenario) to €16 481 (base-case scenario) (€4428 to €19 663 discounted 5%). In AN, the cost per QALY varied from €5296 (best-case scenario) to €64 440 (base-case scenario) (€11 559 or €71 600 discounted 3%), depending on the assumptions used in the analysis.

In Study III, a set of prognostic factors was identified in AN. An impaired follow-up HRQoL score was associated with three baseline risk factors: low self-reported vitality (15D), high scores in eating control and a poor self-reported health status. A low baseline body mass index (BMI) and a high need for support in the eating dimension of the 15D predicted a low follow-up BMI.

In Study IV, the 8-year health-related quality of life in AN and BN continued to improve, but did not achieve the level of the normal population.

In conclusion, the costs of treating AN have been considered high, but in our study, the cost-utility was in the same range as other interventions investigated in our hospital. The cost per QALY in BN was less than the guidelines recommend, and in AN the cost per QALY was in the range the commonly cited guidelines recommend for the adoption of health care interventions, indicating that the treatment of AN and BN in young women is cost-effective and worthwhile. A set of prognostic factors regarding HRQoL was identified and the long-term HRQoL was studied. However, the participants were all female, so the conclusions can only be generalized to female samples, although this is usually the case in research regarding eating disorders. The assessment of HRQoL in ED patients can be a valuable measurement when taking into consideration the long-lasting impact of the disorder on HRQoL. More information on the everyday-life effectiveness of different treatment options should be gathered.

Keywords: health-related quality of life, quality-adjusted life year, cost-utility, anorexia nervosa, bulimia nervosa, eating disorders, adolescent, female, woman, youth

TIIVISTELMÄ

Pohjolainen Veera. Ahmimishäiriötä ja laihuushäiriötä sairastavien naisten elämänlaatu ja hoidon tuloksellisuus

Syömishäiriöt ovat vakavia sairauksia, joihin liittyy korkea kuolleisuus sekä heikentynyt terveyteen liittyvä elämänlaatu. Syömishäiriöiden hoitoa on pidetty kalliina, mutta syömishäiriöiden hoidon kustannusvaikuttavuutta ei ole aikaisemmin mitattu käyttäen laatupainotteisia elinvuosia (Quality adjusted life year eli QALY). Syömishäiriöpotilaiden elämänlaadun pitkäaikaiskehityksestä ei ole tietoa, eikä myöskään tunneta terveyteen liittyvän elämänlaadun muutosta ennustavia tekijöitä.

Tutkimuksen tavoitteena oli mitata ahmimishäiriön ja laihuushäiriön hoidon tuloksellisuutta käyttäen mittarina laatupainotteisia elinvuosia (QALY) ja niiden kustannuksia (osatyöt I ja II). Osatyössä III laihuushäiriön osalta kartoitettiin tekijöitä, jotka ennustivat laihuushäiriöstä kärsivien terveyteen liittyvän elämänlaadun ja painoindeksin (BMI) korjautumista hoidon avulla. Tässä käytettiin apuna Bayesilaista ennustamista. Yhtenä tavoitteena oli myös mitata syömishäiriöpotilaiden terveyteen liittyvän elämänlaadun pitkäaikaiskehitystä (osatyö IV).

Tutkimukseen osallistui 72 laihuushäiriöpotilasta (keski-ikä 23 vuotta) ja 110 ahmimishäiriöpotilasta (keski-ikä 25 vuotta). Tutkimukseen kutsuttiin ne potilaat, jotka olivat aloittamassa hoitoa Helsingin ja Uudenmaan sairaanhoitopiirin (HUS) syömishäiriöyksikössä kesäkuusta 2002 joulukuuhun 2003. Kaikki tutkimukseen osallistuneet potilaat olivat naisia. Syömishäiriöyksikkö on yli 18-vuotiaita hoitava syömishäiriöpotilaiden erityishoidon yksikkö, joka tuottaa palveluita ensisijaisesti HUS-alueen väestölle (väestömäärä on noin 1,5miljoonaa). Hoito on avohoitopainoitteista, mutta myös sairaala- ja päiväsairaalahoitoa voidaan tarjota. Ennen hoidon alkua potilaat vastasivat terveyteen liittyvään elämänlaadun kyselyyn (15D), syömishäiriöoireita kartoittavaan kyselylomakkeeseen (EDI) sekä tutkimusta varten kehitettyyn seurantalomakkeeseen. Seurantalomakkeet postitettiin 6 kuukauden, 2 vuoden ja 8 vuoden kuluttua hoidon alkamisesta. Seurannan aikana potilaat saivat tavanomaista hoitoa syömishäiriöyksikössä, lisäksi hoidon kustannukset poimittiin tietokannasta, johon ne tallentuvat (Ecomed®). Tarkoituksena oli saada lisätietoa syömishäiriöyksikön tavanomaisen hoidon tuloksellisuudesta.

Laatupainotteisten elinvuosien hinta määritettiin käyttäen kahta eri laskelmaa: ns. best-case (ns. optimistisin laskelma) ja base-case (ns. pessimistisin laskelma). Laihuushäiriön ennustetekijöitä kartoitettiin Bayes-mallin avulla, jolla voidaan löytää ennustetekijöitä myös pienissä aineistoissa.

Tutkimustulosten mukaan ahmimishäiriö- ja laihuushäiriöpotilaiden terveyteen liittyvä elämänlaatu oli ennen hoitoa heikentynyt, mutta parani merkitsevästi seurannassa. Ahmimishäiriöpotilaita seurattiin 6 kuukautta(osatyö II) ja laihuushäiriöpotilaita 2 vuotta (osatyö II). QALYn hinnaksi muodostui ahmintahäiriössä €1,455 (optimistisin laskelma) ja €16,481 (pessimistisin laskelma) (5% diskontatut hinnat €4,428 ja €19,663) ja laihuushäiriössä €5 296 (optimistisin laskelma) ja €64 440 (pessimistisin laskelma) (diskontattuna 3% vastaavat luvut €11 559 tai €71 600).

Osatyössä III löydettiin laihuushäiriöön liittyviä ennustetekijöitä: heikentynyt energisyyden kokemus, runsas syömisen kontrollointi ja kokemus huonosta terveydentilasta hoidon aluksi ennustivat, että terveyteen liittyvä elämänlaatu oli edelleen heikentynyt seurannassa. Alkuvaiheen matala painoindeksi ja lisääntynyt tuen tarve syömisessä (15D) ennusti sitä, että painoindeksi ei saavuttanut normaaliarvoa seurannassa.

Osatyössä IV seurattiin syömishäiriöpotilaiden terveyteen liittyvää elämänlaatua 8 vuoden kuluttua hoidon alkamisesta. Terveyteen liittyvä elämänlaatu koheni seurannassa, mutta oli edelleen heikentynyt verrattuna normaaliväestöön.

Vaikka laihuushäiriön hoitoa on pidetty kalliina, tässä tutkimuksessa laihuushäiriön ja ahmimishäiriön hoidon tuloksellisuus QALYjen avulla mitattuna oli samaa luokkaa kuin muiden HUS:n sairaaloiden somaattisten sairauksien hoito. Ahmimishäiriössä QALYn kustannukset olivat jopa pienemmät kuin yleiset ohjeistukset suosittelevat QALY:n kattohinnaksi. Laihuushäiriön osalta QALY:n hinta oli suositusten mukainen.

Yhteenvetona voidaan todeta, että vaikka syömishäiriöpotilaiden hoitoa on pidetty kalliina, oli se QALYjen laskennan avulla kustannusvaikuttavaa. Laihuushäiriössä löydettiin terveyteen liittyvän elämänlaadun ennustetekijöitä ja elämänlaadun pitkäaikaiskehityksestä saatiin lisätietoa. Tutkimukseen osallistuneet potilaat olivat naisia, joten tuloksia ei voi yleistää miehiin. Elämänlaatumittausten käyttäminen syömishäiriöpotilaiden hoidossa voi antaa lisätietoa sairaudesta varsinkin kun tämän potilasryhmän terveyteen liittyvä elämänlaatu oli vielä kahdeksan vuoden kuluttua hoidon alkamisesta heikentynyt. Lisää tietoa tarvitaan erilaisten hoitojen arkivaikuttavuudesta syömishäiriöissä.

Avainsanat: ahmimishäiriö, laihuushäiriö syömishäiriöt, laatupainotteinen elinvuosi (QALY), kustannusvaikuttavuus, elämänlaatu, nuoruusikä

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original studies, referred to in the text by their Roman numerals I–IV.

I Pohjolainen V, Räsänen P, Roine RP, Sintonen H, Wahlbeck K, Karlsson H. Cost-utility in bulimia nervosa. International Journal of Eating Disorders 2010;43:596-602

II Pohjolainen V, Räsänen P, Roine RP, Sintonen H, Koponen S, Karlsson H. Cost-effectiveness of anorexia nervosa treatment in terms of quality adjusted life years. Nordic Journal of Psychiatry. 2016;19:1-5.

III Pohjolainen V, Ryynänen O-P, Räsänen P, Roine RP, Koponen S, Karlsson H. Bayesian prediction of treatment outcome in anorexia nervosa: a preliminary study. Nordic Journal of Psychiatry 2015;69: 210-215.

IV Pohjolainen V, Koponen S, Räsänen P, Roine RP, Sintonen H, Karlsson H. Long-term health related quality of life in eating disorders. Quality of Life Research; 2016;25:2341-6.

ABBREVIATIONS

AN	Anorexia nervosa
BN	Bulimia nervosa
BED	Binge-eating disorder
BMI	Body-mass index
CBT	Cognitive-behavioural therapy
CEA	Cost-effectiveness analysis
COI	Cost-of-illness study
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Eating disorder
EDI	Eating disorders inventory
EDNOS	Eating disorder not otherwise specialized
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD	International Statistical Classification of Diseases and Related Health Problems
IPT	Interpersonal therapy
PRO	Patient-reported outcome
RCT	Randomized controlled trial
SSRI	Serotonin-specific reuptake inhibitors
SMR	Standardized mortality ratio
SD	Standard deviation
QALY	Quality-adjusted life year
QoL	Quality of life
15D	15D instrument

CONTENTS

1 INTRODUCTION

Eating disorders (ED) usually start at the age of 12–24 years and affect adolescent girls and young adult women. EDs are divided into three categories: anorexia nervosa (AN), bulimia nervosa (BN) and atypical eating disorders (EDNOS). Binge-eating disorder (BED) is typically considered to be an EDNOS (Fairburn and Harrison, 2003). Increased mortality (Agras, 2001; Crow et al., 2009; Suokas et al., 2013; Chesnye et al., 2014), severe physical and psychosocial morbidity (Fairburn and Harrison, 2003; Treasure et al., 2010) are often associated with EDs.

Several studies have investigated the treatment and outcome in EDs. However, the functional impairment caused by EDs has previously been overlooked. In the last two decades, there has been increased interest in examining the health-related quality of life (HRQoL) in EDs. QoL comprises many areas and health is only one of its determinants (Bowling, 1996). The health-related quality of life (HRQoL) is a subconcept of QoL. The measurement of HRQoL directly reflects the patient's viewpoint and not that of health-care professionals. HRQoL is often considered in terms of how it is negatively affected, with illness causing impairment and functional limitation and finally disability (Verbrugge and Jette, 1994).

ED patients suffer from impaired HRQoL compared to the general population (Padierna et al., 2000; de la Rie et al., 2005, Abraham et al., 2006, McHugh et al 2007, Jenkins et al., 2011). Although there has been increasing interest in studying HRQoL in EDs, to our knowledge, no studies have followed patients for longer than three years after the start of treatment. Long-term data on the development of HRQoL after treatment are lacking. There is also limited information on the prognostic factors that may predict the treatment outcome measured with the HRQoL. Furthermore, the role of the baseline HRQoL in predicting the AN outcome is poorly understood.

The economic burden of eating disorders is substantial (Simon et al., 2005), although the available information probably underestimates the costs (Stuhldreher et al., 2012). Cost-utility analysis is a type of cost-effectiveness analysis that examines the costs and effectiveness of therapies by using the quality-adjusted life year (QALY) gained as its unit of effectiveness. Cost-utility analyses are therefore considered as important measures both for reporting cost-effectiveness results in the literature and for informing policy decisions on the allocation of health care resources (Pirraglia et al., 2004). The calculation of cost per quality-adjusted life year (QALY) is based on HRQoL scores and the costs of treatment.

To our knowledge, no studies so far have used QALYs as an outcome measure in AN or BN in a naturalistic treatment setting. The aim of Studies I and II was to measure the cost per QALY in BN and AN and compare this with other somatic treatments investigated in our hospital. In Study III, the aim was to find prognostic factors in AN using a Bayesian method. In Study IV, the long-term quality of life of eating disorder patients was measured.

2 REVIEW OF THE LITERATURE

2.1 Bulimia nervosa

Bulimia nervosa (BN) was first named and described by Gerald Russell in 1979 (Russell, 1979), and first included in the Diagnostic and Statistical Manual of Mental Disorders in 1980 (DSM-III, American Psychiatric Association 1980). BN is characterised by recurrent episodes of binge eating and secondly by inappropriate compensatory behaviour (vomiting, purging, fasting or exercising, or a combination of these) in order to prevent weight gain. In BN, self-evaluation is strongly influenced by body shape and weight. People with BN also suffer from a subjective feeling of loss of control over eating when they are binge eating (NICE Guideline, 2004).

2.1.1 Diagnosis of bulimia nervosa

The central features of BN, according to the diagnostic criteria of ICD-10 (10th version of the International Statistical Classification of Diseases and Related Health Problems), are recurrent episodes of overeating in which large amounts of food are consumed in short periods of time (at least twice a week for 3 months), preoccupation with eating and a strong desire or a compulsion to eat, attempts to counteract the fattening effects of food, for instance by self-induced vomiting, the use of appetite suppressants, alternating periods of starvation, and in addition, BN patients have a self-perception of being too fat, with an intrusive dread of fatness

In atypical bulimia nervosa (BN), the same criteria apply as in BN, but not all of the criteria must be fulfilled. In the literature, atypical BN is often described as “broad BN”.

2.1.2 Prevalence

Bulimia nervosa usually starts in young adolescence (age 10–19 years) (Currin et al. , 2005). The prevalence of BN in the literature varies depending on the screening method, population and the diagnostic criteria used. In women, the estimated lifetime prevalence is from 0.9 to 2.9% (Wade et al., 2006; Hudson et al., 2007; Preti et al., 2009). In a large gender-mixed community sample of 14- to 24-years-olds (n = 3021), the cumulative lifetime incidence of BN was 1.2 (Nagl et al., 2016). A Finnish twin study reported the prevalence of bulimia to be about 2.3% in a community sample (n = 2881) (Keski-Rahkonen et al., 2009). In a Finnish sample of adolescents (n = 595), the lifetime prevalence for females age 18 was 0.4% for bulimia nervosa (BN) (Isomaa et al., 2009). In men, the lifetime prevalence of BN has been 0.1–0.5% (Hudson et al., 2007; Woodside et al., 2001). In a large (n = 2230) community cohort of adolescent women, the lifetime prevalence of DSM-5 BN was 0.8% (Smink et al., 2014).

2.1.3 Medical complications of compensatory behaviours

In both AN and BN, severe problems can be caused by compensatory behaviours. For example, purging can cause severe electrolyte and acid-base alterations. Excessive vomiting can result in persistent gastric acid reflux, leading to dysphagia and dyspepsia (Westmoreland et al., 2016), and oesophageal malignancy in BN has even been reported (Dessureault et al., 2002). The repeated exposure to stomach acid can cause dental erosion (Uhlen et al., 2014). Parotid gland enlargement, sialadenosis, is a common feature of self-induced vomiting (Coleman, 1998).

The most dangerous medical complication of self-induced vomiting relates to electrolyte and acid-base changes. Metabolic alkalosis and hypokalaemia are the most common abnormalities. With vomiting, this is due to the loss of both acid and potassium in the vomitus. The potentially severe degrees of hypokalaemia can cause cardiac arrhythmias and can be one of the causes of mortality in BN (Crow et al., 2009; Westmoreland et al., 2016). BN patients can also abuse syrup of ipecac to accomplish vomiting. Ipecac contains a cardiac toxin (emetine)

that can cause irreversible cardiomyopathy and severe congestive health failure (Ho et al., 1998).

Excessive laxative abuse can cause hypokalaemia. In addition, laxative abuse can cause rectal prolapse, diarrhoea, haemorrhoids and haematochezia (Xing et al., 2001; Malik et al., 1997). Chronic laxative abuse can result in permanent harm to the peristalsis of the colon. Consequently, the colon is converted into an inert tube and severe constipation ensues, which may necessitate a colectomy (Joo et al., 1998).

2.1.4 Psychiatric comorbidities

In a large, nationally representative, population-based study conducted by Hudson et al. (2007), it was found that among individuals with an eating disorder, those with BN were at highest risk of a comorbid disorder (94.5% of the individuals with BN had at least one comorbid disorder). BN is often associated with affective disorders (McElroy et al., 2006;), with 80–90% reporting at least one episode during their lifetime (Godart et al., 2015), and with alcohol misuse (Gadalla et al., 2007; Bulik et al., 2004a).

There is also an association with personality disorders (Braun et al., 1994, van Hanswijck de Jonge et al 2003). In a study of BN and personality disorders in college women, 61% of BN met the criteria for a personality disorder. The most typical of these was borderline personality disorder (34.7%) (Schmidt and Telch, 1990). Evidence suggests that the course of illness (Thompson-Brenner et al., 2008) and treatment outcomes in BN (Hayes et al., in press) are associated with personality constructs. Researchers have also identified a "multi-impulsive BN group" (Lacey and Evans, 1986; Fichter et al., 1994) categorized by three or more risky behaviours (alcohol abuse, drug abuse, self-harm, suicide attempts, stealing and/or sexual promiscuity) (Myers et al., 2006).

2.1.5 Mortality

In a meta-analysis, the weighted mortality rate (i.e., deaths per 1000 person-years) in BN has been 1.7 and the standardized mortality ratio 1.93 (Arcelus et al., 2011). In a Finnish study, the hazard ratio (HR) for suicide was elevated in broad BN (HR 6.07; 95% CI 2.47–14.89) (Suokas et

al., 2013). In a study conducted in the US, the crude mortality rate for BN was 3.9 and the mortality rate was elevated both for all causes and suicide (Crow et al., 2009).

2.1.6 Treatment of bulimia nervosa

There is a strong evidence-base that in BN, cognitive-behavioural therapy (CBT) and interpersonal psychotherapy (IPT) reduce binge eating (Hay et al., 2009). However, the binge remission rates at the end of CBT are only 30–40% (Hay et al., 2009). IPT is as efficacious as CBT, but it has shown a slower response of symptom change than CBT (Shapiro et al., 2007; Hay et al., 2009). Both group and individual therapy are effective. People over 18 years old who receive CBT will probably benefit from taking serotonin-specific reuptake inhibitors (SSRI) (NICE Guideline, 2004; Hay et al, 2001). SSRI medication during 8 weeks can reduced binge eating by 50% (Balcaltchuk and Hay, 2003). Self-help approaches that used highly structured CBT treatment manuals have been promising (Hay et al., 2009).

2.1.7 Prognosis of bulimia nervosa

Only a minority of BN cases are detected by healthcare providers (Mustelin et al., 2015; Keski-Rahkonen and Mustelin, 2016). Keel and Brown (2010) examined studies conducted between 2004–2010 and found that the remission rates for bulimia nervosa vary considerably depending on the length of the follow-up period. The lowest rates (27–28%) were reported with a one-year follow-up, and the highest rates (up to 74%) were reported in studies with a 5- to 20-year follow-up. One study (Ben-Tovim et al., 2001) assessed the five-year outcome based on the Morgan-Russell-Hayward criteria: on follow-up, 76% of those with a history of treatment had a good outcome and only 2% had a poor outcome. In a twelve-year follow-up study by Fichter and Quadflieg (2004), it was found that the majority of patients (70%) were in remission, while 23.3% suffered from an eating disorder. They also found the total EDI scores to be worse at the two-year follow-up than on discharge, but the scores had reached the discharge level at six years and had significantly further improved at the 12-year follow-up. In a study by Keel and

colleagues following 222 BN patients for a mean of 11 years, about 70% of the patients were in full or partial remission, but 11% still met the criteria for BN (Keel et al., 1999). In a population-based study by Fairburn and colleagues (2000) examining the natural course of BN, there was a significant improvement in the EDE score over a period of five years.

Across studies on BN, psychiatric comorbidity and general psychiatric symptom severity have emerged as poor prognostic indicators (Fichter et al., 2004; Clausen, 2008). Avoidant personality disorder (Grilo et al., 2007) and a family history of alcohol abuse (Bogh et al., 2005) have predicted a worse outcome.

2.2 Anorexia nervosa

Anorexia nervosa-like syndromes date to the practice of fasting by medieval saints, but the clinical description first appeared in the 17th century by Morton (Silverman, 1983). The British physician William Gull and the French physician Henri Laseque provided the first modern accounts of the condition, the essential features of which have remained unchanged to this day.

People suffering from anorexia nervosa (AN) have a drive to thinness, which results in weight loss and a refusal to maintain a normal body weight. In AN, a widespread endocrine disorder develops as a consequence of poor nutrition (NICE Guideline, 2004). AN patients additionally suffer from many medical problems, such as osteoporosis, cardiovascular problems and psychological problems (Agras, 2001).

2.2.1 Diagnosis of anorexia nervosa

The central features of AN, according to the ICD-10 diagnostic criteria, are weight loss, or a lack of weight gain in children, leading to a body weight at least 15% below the normal or expected weight. The weight loss is self-induced, the patients suffer from a self-perception of being too fat and a dread of fatness, and in addition, a widespread endocrine disorder occurs, manifesting in females as a amenorrhoea and in males as a loss of sexual interest and potency.

The diagnosis of atypical anorexia nervosa in the ICD-10 (F50.1) follows the same criteria as AN (F50.0), but the patients need not fulfil all the criteria. Several studies have found that the distinction between AN (50.0) and atypical AN (F50.1) is associated with differences in the

treatment outcome, clinical presentation and mortality (Dellava et al., 2011; Suokas et al., 2013; Silen et al., 2015).

2.2.2 Prevalence

AN usually develops during adolescence and the highest incidence occurs at the age of 10–19 years (Currin et al., 2005). In a large community-based study (n = 3021), the earliest onset of EDs appeared in those with symptomatic AN, with a considerable proportion of individuals already showing symptoms before 13 years of age (Nagl et al., 2016). Estimates of the prevalence and incidence of AN depend on the screening method, the population in question and the diagnostic criteria used. In the literature, the lifetime prevalence of AN among women has varied from 0.3–0.9% (Hudson et al., 2007; Preti et al., 2009; Swanson et al., 2011; Smink et al., 2012), but higher estimates (1.2–2.2%) have also been reported. In twin studies, the prevalence has been higher (Keski-Rahkonen et al., 2007; Smink et al., 2012), and in a Finnish population-based sample (n = 1863), the prevalence of AN was 2.1% (Lähteenmäki et al., 2014). In a large gender-mixed community sample of 14- to 24-year-olds (n = 3021), the cumulative lifetime incidence of AN was 1.7% (Nagl et al., 2016). In adolescents (n = 595), the lifetime prevalence for females aged 18 years was 2.6% for anorexia nervosa (AN) (Isomaa et al., 2009). In men, the lifetime prevalence of AN was estimated to be 0.24% (Raevuori et al., 2009). However, changes in diagnostic definitions and different operationalizations can have an impact on the prevalence (Brown, 2014). In a large (n = 2230) community cohort of adolescent women, the lifetime prevalence of DSM-5 anorexia nervosa was 1.7% (Smink et al., 2014).

2.2.3 Medical complications in AN

Weight loss and malnutrition in AN can cause complications in almost every body system (Westmoreland et al., 2016). Complications related to purging are also common in AN, and are discussed in the section concerning complications related to BN.

Sudden cardiac death along with other medical complications and suicide account for approximately 60% of AN-related deaths (Westmoreland et al., 2016). In the cardiac system, bradycardia is noted and hospitalization is recommended for a heart rate of less than 40 beats

per minute (käypä hoito, 2014). Patients may additionally suffer from prolongation of the QTC interval (<500 ms) in electrocardiography, but this has actually been quite rare in the absence of contributing factors (Faccini et al., 2006; Krantz et al., 2011). Severe anorexia nervosa can lead to left ventricular atrophy and pericardial effusions, which are generally reversible with refeeding. However, one MRI study demonstrated a myocardial scar in AN patients, which can lead to malignant arrhythmias (Oflaz et al., 2013). In the gastrointestinal system, slowed gastric emptying, gastroparesis, acute gastric dilatation and even superior mesenteric artery syndrome have been demonstrated in AN (Benini et al., 2004; Mascolo et al., 2015). In addition, elevated liver transaminases frequently occur as a result of malnutrition (Miller et al., 2005).

The effects of AN on the haematological system cause anaemia, leukopenia and thrombocytopenia (Hutter et al., 2009). Osteoporosis is also common in AN, increasing the risk of bone fractures later in life (Lucas et al., 1999). Unfortunately, no treatments are currently specifically approved for osteoporosis in AN; however, weight gain and the resumption of menses are associated with improved bone density (Miller et al., 2006). Osteoporosis is one of the complications of AN, and may be lead to irreversible damage even after recovery (Westmoreland et al., 2016). The effects on the endocrine system increase the risk of amenorrhoea and can cause infertility (Jacoangeli et al., 2006). Hypoglycaemia can occur in severe AN as a result of depleted hepatic glycogen stores, and is a poor prognostic sign (Rich et al., 1990). The medical complications related to purging are discussed in detail in the section concerning medical complications in BN.

A significant global loss of brain volume has also been observed in AN in both grey matter and white matter in several studies, including two recent meta-analyses (Titova et al., 2013; Seitz et al., 2014). The mechanisms of brain volume reduction are largely unknown (Seitz et al., 2015). During weight gain, however, a significant volume recovery has been noted (Ehrlich et al., 1998; Mainz et al., 2012).

In the nutritional rehabilitation in AN, a rare side effect of refeeding syndrome should be carefully considered (Marzola et al., 2013). Refeeding syndrome is caused by the rapid refeeding of someone in a state of starvation (BMI under 12), and is characterized by hypophosphataemia, hypomagnesaemia, hypokalaemia, glucose intolerance, fluid overload and thiamine deficiency. The clinical consequences can include cardiac arrhythmia, hypotension, rhabdomyolysis, respiratory failure and coma (Hearing, 2004).

Many of the cognitive deficits in anorexia nervosa are restored after weight recovery. However, some abnormalities in executive function remain after weight restoration (Tchanturia

et al., 2002). In addition, reproductive health outcomes are compromised in women with a history of EDs (Linna et al., 2013).

2.2.4 Psychiatric comorbidities

There is a significant comorbidity of affective and anxiety disorders with anorexia nervosa (Halmi et al., 1991; Jacobi et al., 2004b; Blinder et al., 2006; Hudson et al., 2007; Lähteenmäki et al., 2014). In a female inpatient sample, 97% evidenced one comorbid diagnosis. Comorbid mood disorder was the most common (94%), while 56% of inpatients evidenced anxiety disorders and 22% evidenced substance use disorders. There were no differences across eating disorders in depression or anxiety disorder, but alcohol abuse/dependence was twice as likely with BN (Blinder et al., 2006). The National Comorbidity Survey Replication (NCS-R) revealed that more than half (56.2%) of respondents with AN met the criteria for at least one other mental disorder (Hudson et al., 2007), and similar results have been found in a Finnish study (Lähteenmäki et al., 2014).

AN patients also suffer from autistic spectrum disorders, attention-deficit hyperactivity disorder (Wentz, 2005) and personality disorders (typically C-cluster: obsessive-compulsive, dependent, and avoidant personality) (Johnson and Wonderlich, 1992). In a sample of ED individuals, 35% of those with AN met the criteria for obsessive-compulsive disorder (OCD) (Thornton and Russell, 1997). The prevalence in ED samples of personality disorder varied from 21% to approximately 90% for AN and BN in a meta-analysis (Rosenvinge et al., 2000).

2.2.5 Mortality

AN patients suffer from one of the highest mortality rates of all psychiatric disorders (Chesnye et al., 2014). In a meta-analysis, the standardized mortality rate in AN was 5.86 (Arcelus et al., 2011) and in a large prospective clinical longitudinal study it was 5.35 (Fichter and Quadflieg, 2016). Most deaths due to AN are a direct consequence of starvation-related complications, while one in five deaths in AN result from suicide (Royal College of Psychiatrists, 2012). In a follow-up study in the Helsinki and Uusimaa Eating Disorder Clinic, the mortality risk (hazard

ratio, HR) in broad anorexia of all causes was 6.51 and the risk of suicide was elevated (HR 5.07) (Suokas et al., 2013).

2.2.6 Treatment of anorexia nervosa

Evidence-based recommendations for the treatment of AN are scarce. These recommendations emphasise the importance of a multidisciplinary approach, including medical, nutritional, social and psychological components (NICE Guideline, 2004; American Psychiatric Association Practice guidelines for the treatment of patients with eating disorders., 2006; Käypä hoito 2014).

Evidence also suggests that in AN, weight should be restored to the level of the resumption of menses (90% of standard body weight) to have a better prognosis (Golden et al., 1997). The guidelines agree that most people with AN can be treated as outpatients, but that day-patient and inpatient services are needed for those with more severe illness and those who do not improve with outpatient care. In a multicentre randomized trial, Herpertz-Dalman and colleagues (2014) reported that a stepped care approach including day-patient treatment was equally effective and less costly compared to inpatient treatment in non-chronic adolescent AN.

In adolescent patients with AN, there is clear and growing evidence to support the efficacy of family treatment compared with individual-based approaches (Lock, et al., 2010, 2015). The evidence supports family-based treatment with a focus on eating disorder behaviour and weight gain (Lock, 2015).

In adult patients with AN, several treatment studies have been published, reporting substantial weight gain and improvements in the eating disorder and general psychopathology at the end of treatment and on follow-up (Whitney et al., 2012; Schmidt et al., 2012, 2015; Zipfel et al., 2014, 2015). The largest of these trials compared three different treatments: focal psychodynamic psychotherapy (FPT), enhanced cognitive behaviour therapy (CBT-E) and optimized treatment as usual, including psychotherapy as well as medical care by the family doctor (Zipfel et al., 2014). Weight gain was similar in all three groups, but in FPT it proved advantageous in terms of recovery at 12 months, while CBT-E was more effective with respect to the speed of weight gain. A novel anorexia nervosa-specific outpatient therapy (Maudsley Model of Anorexia Nervosa Therapy for Adults, MANTRA) has been compared with Specialist

Supportive Clinical Management (SSCM)(Schmidt et al 2012). The overall outcome did not differ between groups, but patients preferred MATRA to SSCM, and patients with more severe illness experienced a greater weight gain in the MANTRA group (Schmidt et al., 2015). In summary, the evidence base for the treatment of adults with anorexia nervosa is advancing, but no specific approach has shown clear superiority(Hay et al 2015). The common elements of the AN psychotherapeutic approach are focused on weight regain and nutritional rehabilitation (Hay 2014)

The evidence regarding pharmacotherapies is scarce. No strong evidence lends support to drug treatment in either the acute or maintenance phases of the illness. Studies have investigated fluoxetine in the prevention of relapse in AN, but the evidence base for this is weak (Walsh, 2006; NICE Guideline, 2004). There has been interest in the potential use of atypical antipsychotic drugs. The idea is that by reducing anxiety symptoms and distorted cognition, resistance to weight gain decreases. Small initial randomised studies have reported decreases in obsessive symptoms and an increased rate of weight gain (Bissada et al., 2007; Bissada et al., 2008). However, larger trials are necessary determine whether these drugs are beneficial, despite the potential increase in the QTc interval with the concomitant risk of cardiac arrhythmias.

2.2.7 Prognosis of anorexia nervosa

The course of anorexia nervosa is very variable (Treasure and Schmidt, 2002). Many people with eating disorders who have been detected in community studies have not sought treatment (Hudson et al., 2007, Keski-Rahkonen et al 2007). There is no good evidence on the prognosis of those AN patients who do not access formal medical care (Treasure and Schmidt, 2002).

Steinhausen (2002) summarised 119 treatment studies covering 5590 patients, finding that, on average, only 46.9% of the surviving patients fully recovered, while 33.5% improved and 20.8% developed a chronic course of the disorder (Steinhausen, 2002). A one-third cross-over to BN has also been observed in AN (Eddy et al., 2008). The crude mortality rate was 5.0 in the study by Steinhausen et al. (2002). The SMR in AN appears to be higher than in schizophrenia, bipolar or unipolar depression (Arcelus et al., 2011), and one of the highest in the field of psychiatry (Chesnye et al. 2014).

In AN, few prognostic factors have reliably been identified. Negative prognostic factors for AN are a longer duration of illness before treatment and a longer duration of treatment or need

for inpatient treatment (Fichter et al., 2006; Eisler et al., , 2007; Papadopolous et al., 2009). Prognostic indicators for AN appear to be closely associated with the severity and duration of AN (Keel et al., 2010). Premorbid depressive symptoms in AN are also associated with a poor outcome in the general population (Keski-Rahkonen et al., 2014). Since the highest incidence of AN occurs between 10 and 19 years of age (Currin et al., 2005), this condition can potentially disrupt optimum growth and development. AN can also cause educational disturbances (Byford et al., 2007), which can lead to difficulties in independent living in 20% of cases up to 10–20 years after the onset of the illness (Hjern et al., 2006).

2.3 Other eating disorders

Some people suffer from eating disorders that do not meet the precise diagnostic criteria for AN or BN, but closely resemble these conditions (Fairburn and Harrison, 2003). In Europe, these are often termed 'atypical eating disorders' (Fairburn and Harrison, 2003), the equivalent American term being 'eating disorders not otherwise specified' (EDNOS) (American Psychiatric Association, 1994). EDNOS comprises the most common subgroup of eating disorders in both clinical and community samples (Smink et al., 2013). Binge-eating disorder (BED) is typically considered a part of EDNOS, and is the most common eating disorder in the EDNOS subgroup (Fairburn and Harrison, 2003).

2.3.1 Binge-eating disorder (BED)

The occurrence of binge-eating episodes in the absence of compensatory behaviours is the core feature of BED. The disorder is often seen in obese individuals, but it differs from obesity in terms of psychopathology and weight and shape concerns (Wonderlich et al., 2009). In BED, the lifetime prevalence varies from 1.9 to 3.5% (Hudson et al., 2007; Preti et al., 2009; Swanson et al., 2011). In men, the prevalence varies from 1.1–3.1% (Hudson, 2007; Striegel-Moore and Franko, 2003). In a Finnish community-based study concerning young adult women (ages 22–27), the lifetime DSM-5 prevalence was 0.7% (Mustelin et al., 2015). The mortality risk in BED is elevated and an SMR of 2.3 is described in the literature (Fichter et al., 2008).

2.4 Aetiology of eating disorders

The aetiology of eating disorders is considered to be multifactorial (Cooper and Steere, 1995). It depends on individual vulnerability, consequent on the presence of biological or other predisposing factors, their exposure to particular provoking risk factors (Jacobi et al., 2004a) and on the operation of protective factors, whether or not a person develops an eating disorder (NICE Guideline, 2004).

2.4.1 Genetic risk factors

Behavioural genetic data have consistently indicated that both genetic and environmental influences contribute to eating symptoms (Culbert, et al. , 2015). The division into genetic and environmental risk factors is somewhat artificial, because parental mental disorder, for example, is a genetic risk factor, but also an environmental factor in that it affects the emotional atmosphere in the family (Nomura et al., 2002). The combined genetic and environmental effect is called gene–environment interaction. The effects of environmental factors may also transfer without changes in the DNA sequence; this is called epigenetics (Foley et al., 2009; Liyanage et al., 2014).

Large twin studies have established that AN, BN and BED are *heritable* (Bulik et al., 2016). Ylimaz et al. (2015) reported the replicated twin-based heritability estimates for AN (0.48–0.74) and BN (0.55–0.62). Nonshared environmental effects generally account for the remaining variance (Culbert, et al., 2015).

Despite significant methodological advances in the study of genetic associations over the past two decades, we still know relatively little about the specific genes that contribute to eating disorders. Five genome-wide association studies (GWAS) have been conducted for AN or disordered eating (Wade et al., 2013; Culbert et al.,, 2015), but no gene variant has met the significance threshold for multiple comparisons. Candidate gene association studies have been used to examine genes in *neurobiological systems* (e.g. serotonin (5HT), dopamine, brain-derived neurotrophic factor) (Culbert et al., 2015). Possible polymorphisms of the *5-HT2A* (Gorwood et al., 2003) and *5-HTTLPR polymorphic region of the serotonin transporter gene* (Calati et al., 2011) appear robust candidates for AN. Evidence for genetic and environmental effects has also

emerged from developmental twin studies. The magnitude of genetic influences on disordered eating symptoms in females varies according to *age and pubertal status*. *Ovarian hormones* have been proposed as a possible mechanism underlying developmental changes in the genetic risk in girls (Ostlund et al., 2003).

In a Swedish register-based study, it was found that when one or both parents had a *lifetime history of psychiatric disorder,* the offspring were at increased risk of developing an eating disorder (Bould et al., 2016). The nature of suicidality in eating disorders has also been examined in a Swedish population study (Yao, 2016). An increased risk of suicide attempts was recorded among individuals with eating disorders and among individuals without eating disorders who had a relative with an eating disorder, suggesting that *suicidality* may be due to familial liability for the association between eating disorders and suicide (Yao et al., 2016). The co-occurrence of eating disorders and other psychiatric conditions is partly due to shared genetic factors (Bulik et al., 2016).

Gene–environment interplay

Parental factors (e.g. *parental pressures and criticism; low parental contact*) and *abuse history* have been identified as retrospective correlates of eating pathology (Jacobi et al., 2004a). Abuse history is often considered a risk factor because of some retrospective reports, and childhood abuse was demonstrated to prospectively predict an elevated risk of disordered eating and eating disorder onset in a longitudinal study (Johnson et al., 2002). The interactions between these environmental experiences and biological factors have been explored in some studies. The short allele of 5-HTTLPR has been shown to interact with *parenting style, e.g. criticism, underinvolvement and physical abuse* in the prediction of AN, bulimic symptoms and the drive for thinness (Culbert, et al., 2015). These data provide initial evidence that environmental experiences may serve to potentiate the risk of eating disorders, particularly in individuals who are biologically vulnerable. *Epigenetic alterations in dopaminergic functioning* may also be linked to eating disorders (Culbert, et al., 2015; Groleau et al., 2014).

2.4.2 Environmental risk factors

2.4.2.1 Biological risk factors

Prenatal stress following maternal bereavement is associated with an increased overall risk of EDs in adolescent girls and young women (Su et al., 2016). *Early insults to the central nervous system* may contribute to the onset of AN, at least in a subpopulation of individuals (Favaro et al., 2011a; Cnattingius, 1999). Perinatal factors, e.g. *pregnancy and delivery complications*, *hypoxia* and *signs of retarded foetal grow* (Favaro, 2011b), as well as *multiple births and a lower gestational age*, have also been associated with an elevated risk of developing AN (Goodman, 2014). In BN, there is evidence that *restricted growth* and a *smaller birth size* predict later BN (Favaro et al., 2006). In a Swedish data set (Goodman et al., 2014), a contrary finding was that a *higher birth weight* predicted BN. This may reflect the significance of early metabolic programming in the tendency to gain weight, which is also relevant in BN (Skilton et al., 2014). The overall effect of prenatal/perinatal factors on the total risk of EDs appears to be relatively small. It is likely that if there are early prenatal/perinatal risk factors, they operate in conjunction with other individual or environmental factors and, depending on the combination of risk factors, the outcome varies (Raevuori et al., 2014a).

Puberty and adolescence are characterized by profound changes, vulnerabilities and the transition to adulthood, and they represent the period of first onset of AN (Zipfel, 2015). A possible explanation for the crucial role of puberty in the onset of AN might lie in *hormonal changes* and *dysregulations that interact with neurotransmitter functioning, brain maturity and genetic* factors (Herpertz-Dahlman et al., 2011).

The rate ratio of the lifetime prevalence of AN and BN in *females* is substantially higher than in males (sex ratio ranging from 1:10 to 1:16) (Hoek, 2006; Nagl et al., 2016). On the other hand, the risk of eating disorders has also been shown to be increased in some *somatic illnesses, e.g. type 1 diabetes* (Tiller, 1994; Jones et al., 2000; Arigo et al., 2012), and several *autoimmune diseases* with different genetic backgrounds (Raevuori et al., 2014b). There is a highly increased risk of *type 2 diabetes* in patients with binge eating disorder and bulimia nervosa (Raevuori et al., 2015). *Paediatric autoimmune neuropsychiatric disorders* associated with streptococcal

infection (PANDAS) is a process whereby a streptococcal infection leads to the onset of anorexia nervosa through a postulated autoimmune mechanism (Vincenzi et al., 2010).

2.4.2.2 Psychosocial risk factors

Personality traits have received significant attention in aetiological models of eating disorders (Lilenfelc et al., 2006). *Negative emotionality* predicts the development of eating pathology. Similarly to eating disorders, personality traits have been shown to be heritable. The remaining variance is typically explained by nonshaired environmental factors (Polderman et al., 2015). *Perfectionism* also increases the risk of eating disorders. Perfectionism interacts with *body dissatisfaction to predict the drive for thinness.* Results from twin studies suggest that genetic, rather than environmental factors are most important (Wade and Bulik, 2007). *Inhibitory control deficits* appear to be correlates of EDs (Culbert et al., 2015). *Neurocognitive flexibility* is also impaired in AN, and it may persist (Tchanturia et al., 2012).

The environment also carries other risk factors. In a large register study in Sweden, a *higher level of parental education* independently predicted a higher rate of ED in females, but not in males (Ahren et al., 2013). However, in a Finnish study, adolescent eating disorders were not associated with the socio-economic status of the family (Litmanen et al., 2016). In addition, *neglect and physical and sexual abuse* increase the risk of developing an eating disorder (Treasure et al., 2010). *Negative self-evaluation, elevated weight and shape concerns, general psychiatric morbidity* (Jacobi et al., 2004), *depressive disorder and generalized anxiety disorder* (Sihvola et al., 2009) are also risk factors of EDs.

2.4.3 Sociocultural context

The increase in AN in low-income and middle-income countries suggests that cultural transitions associated with industrialisation, globalisation and urbanisation might be associated with environmental risk constellations for the development of AN (Smink et al., 2012). The adoption of the so-called Western lifestyle, including thin ideal internalisation, might be part of

this constellation. In addition, food-related and weight-related harmful experiences can have an influence on developing an ED. The rates of BN symptoms have also increased following exposure to Western influences (Becker et al., 2002). The excess value placed on thinness encourages extreme dieting and weight control practices. Criticism focused on shape, weight and food issues increases the risk of developing an eating disorder (Wade et al., 2007).

Despite these sociocultural pressures to be thin, the incidence of AN is relatively low (Schmidt, 2003). The adoption of thin ideal internalisation could simply increase the number of individuals engaging in strict dieting and excessive exercise, which can then trigger eating disorders in genetically susceptible individuals (Zipfel et al., 2015). Twin studies have demonstrated that internalization of the thin ideal is accounted for by individual differences in both genetic and environmental factors (Suisiman, 2012, 2014).

2.4.4 Neurobiological factors as a result of disordered eating behaviours

As a result of starvation and disturbed eating behaviours, many biological disturbances emerge. However, some biological findings are causally linked as risk or maintaining factors (Treasure et al., 2010). Starvation is associated with many behavioural and psychosocial disturbances. During starvation, the brain shrinks, causing rigidity, emotional dysregulation and social difficulties (Keys et al., 1950). There are profound disturbances of brain serotonin (Kaye et al., 2005), neuropeptide systems (Frank et al. 2005) and brain neurocircuitry (Muhlau et al., 2007). During weight gain and brain mass restoration, many symptoms resolve (Castro-Fornieles et al., 2009).

Abnormal changes in the central control of appetite have a role in the risk and maintenance of eating disorders (Treasure et al., 2010). In the models of binge eating in laboratory rodents, eating disorder behaviours have been seen to affect the drive system of the central control of appetite (Avena, 2007; Boggiano et al., 2007). In these studies, researchers have replicated the conditions implicated in the increase in binge eating and produced animals with an addiction to food.

Abnormalities in both illness-related (food and body shape) and non-illness-related information processing have been detected in eating disorders. An attentional bias is evident towards food and body shape (Lee, 2004) associated with increased activation in distributed

neural networks connected with self-regulation and hedonic motivation (Kaye et al., 2009; Van den Eynde and Treasure, 2009). These functional anomalies can maintain eating disorder behaviours. For example, impaired social and emotional regulation could cause isolation.

2.4.5 Protective factors

Protective factors identified in studies include low BMI, healthy eating attitudes (Westerberg-Jacobson, 2010), an accepting attitude towards body size and a positive self-evaluation (Gustafsson et al.,2009). Parent-adolescent connectedness and frequent family communication have also been identified as protective factors for adolescent dieting and eating disorder symptoms (Fonseca et al., 2002). Greater parent-adolescent connectedness and a greater family meal frequency have also been identified as significant prospective protective factors for dieting, binge eating and purging in adolescent girls (Berges et al., 2014; Haines et al., 2010).

2.5 Adolescence

Adolescence is a transitional stage from childhood into adulthood during which the individual undergoes many physiological, psychological, cognitive and social changes (Aalberg, 2016). Adolescence is initiated by pubertal onset and can be divided into three periods: early adolescence (12–14 years), middle adolescence (15–16 years) and late adolescence (17–22 years) (Richter, 1998). Each of these periods has certain developmental tasks, which are the achievement of biological and sexual maturity, the development of personal identity, the development of intimate sexual relationships, and the establishment of independence and autonomy (Christie and Viner, 2005). Adolescence is characterized by major changes in the neural systems that serve higher subcognitive functions, reasoning and interpersonal interactions, cognitive control of emotions, risk-versus-reward appraisal and motivation. It is precisely these changes that, when suboptimal in timing or magnitude, increase the risk of cognitive, affective and addictive disorders (Paus et al., 2008). In the field of EDs, studies have revealed that EDs are associated with early maturation, suicidal behaviour, body dissatisfaction and conflicts in family relationships, especially with BN, and psychosexual difficulties and few social contacts with AN (Ruuska, 2006).

In a Finnish study on adolescents, mid-adolescent girls showed significantly greater body dissatisfaction than boys. Adolescents with underweight appeared to be most satisfied and those with overweight and obesity most dissatisfied with their bodies. Body dissatisfaction and self-esteem were negatively correlated, and body dissatisfaction was associated with abnormal eating. (Mäkinen, 2015).

2.6 Quality of life

Modern medicine has traditionally focused on assessing patients through objective measures. However, outcomes cannot be solely assessed in objective terms, as such indicators do not explain how people perceive and experience their lives. Recently, the focus in medicine has been redirected to the broader personal and social context of the person with the disease (Higginson et al., 2001). Quality of life has become an important adjuvant and alternative tool in clinical assessment (Orley et al., 1998).

Since 1948, when the World Health Organization (WHO) defined health as being not only the absence of disease and infirmity but also the presence of physical, mental and social well-being, quality-of-life issues have become more important in health care practice and research (WHO, 1948). There has been a nearly exponential increase in clinical studies measuring quality-of-life since 1973 (Testa and Simonson, 1996). The World Health Organization (WHO) defines quality of life as "an individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (The WHOQOL Group, 1998).

One of the reasons behind the rapid development of quality of life measures in healthcare has been the growing recognition of the importance of understanding the impact of healthcare interventions on patients' lives rather than just on their bodies (Addington-Hall and Kalra, 2001). Quality of life (QoL) is becoming an increasingly important outcome of healthcare for several reasons. Subjective valuations, autonomy and the needs of patients are increasingly respected (Saarni et al., 2010). Patients are interested in their quality of life after an intervention and they may actually appreciate this endpoint more than clinicians do. This has

led clinicians and researchers to quantify the impact of specific interventions (Spertus et al., 2002).

Defining and measuring quality of life is complicated. When trying to define and measure QoL, we need to take into account both objective life conditions and subjective personal appraisals. What is important to each person varies. A synthesis of these perspectives provides a model of quality of life, which integrates objective and subjective indicators and individual values across a broad range of life domains (Felce, 1997). Considerable agreement exists that quality of life is multidimensional. It can be categorised within five dimensions: physical well-being, material well-being, social well-being, emotional well-being, and development and activity (Felce and Perry, 1995).

2.7 Health-related quality of life

2.7.1 Theory of health-related quality of life

WHO supports the consensus view that health is more than a matter of the absence of a specific disease or injury. It is also the presence of certain threshold levels of the ability to carry out physical and mental actions and tasks in the current environment (WHO, 2002). During the last three decades, there has been general acceptance of an approach to describing health states of individuals in terms of multiple domains of health, and in developing self-report instruments that seek information on each of these domains (Hunt et al., 1981; Ware et al., 1993). In order to measure and report on the health of populations or individuals, under any of the three views outlined above, it is necessary to develop a valid, reliable and comparable way to measure the health status. This requires the following: a classification of the health state domains, and specification of a set of domains necessary and sufficient to describe health states for measurement purposes; specification of what we are measuring in each domain; a common understanding of what is full health versus exceptional talent in any given domain; and, if we wish to construct summary measures of the average level of population health, a method to place a single cardinal value on the overall level of health associated with a health state defined in multiple domains (WHO, 2002).

2.7.2 The concept of Health-related quality of life

Health-related quality of life (HRQoL) is a subconcept of QoL: HRQoL tries to capture the aspects of QoL that health and ideally also healthcare can influence. HRQoL is a fairly broad, multidimensional concept that includes symptoms of the disease or health condition, treatment side effects, and functional status across physical, social and mental health life domains (Revici et al., 2014). In addition to its multidimensional nature, a core component of the definition is the emphasis on the subjective, patient perspective. There is also increasing recognition that HRQOL is a subjective matter, and how these components are affected by illness and treatment should therefore be assessed by the individuals themselves (Slevin et al., 1988).

HRQoL outcomes are currently a large subset of an even broader set of outcomes that have come to be referred to as patient-reported outcome (PRO) measures (Revici, 2014). PROs are defined as any report of the status of a patient's health condition or other clinical outcome that comes directly from the patient without interpretation from a clinician or anyone else. The use of PROs in research is well established (Black et al., 2016). There is a consensus that health outcome evaluations that include PROs along with clinician-reported outcomes and administrative data are necessary to inform clinical and policy decisions.

2.8 Health-related quality of life in eating disorders

Several studies have investigated the abnormal eating patters in eating disorders, but studies also taking into account the patients' perception have only in recent decades been under interest. Eating disorders are serious disorders (Klump et al., 2009) affecting young individuals for a long time, and it is crucial to gain more information on the overall well-being of these patients and how the treatment affects their HRQoL. The health-related quality of life of the caregivers of ED patients has also been under investigation in recent years (Martin et al., 2011).

Studies have shown that ED patients suffer from impaired QoL compared to the general population (Padierna et al., 2000; De la Rie et al., 2005) (Table 3). This impairment in QoL is

greater than in many psychiatric disorders (for example mood disorders) or physical conditions (for example coronary angina) (Keilen, 1994; De la Rie et al., 2005; Jenkins et al., 2011). There have not been any differences in diagnostic groups concerning HRQoL (Winkler et al., 2014), but impairments in HRQoL are associated with the severity of ED symptoms (Bamford and Sly, 2010). After the treatment of ED, former patients have still demonstrated lower QoL than population norms (de la Rie et al., 2005) (Table 4). In one study, patients' QoL scores improved following treatment and were maintained at a one-year follow-up, but still remained poorer than those of a female student control group (Abraham et al., 2006). One reason for this could be that the changes seen immediately following treatment may be smaller than those reported on follow-up, reflecting a greater psychological change over the longer-term (Abraham et al., 2006). Binge eating and/or the use of purging behaviours has predicted a poorer quality of life in some studies (Jenkins et al., 2011; Gonzales-Pinto et al., 2004). Studies following patients after treatment completion are scarce (Table 4). A recent meta-analysis emphasised that AN, BN and BED have a serious impact on the patient's HRQoL and are also associated with increased healthcare utilization and healthcare costs. According to the authors, the limited evidence suggests that further research is warranted to better understand the differences in long-term HRQoL and the economic burdens of AN, BN and BED (Agh et al., 2016).

2.9 Measurement of health-related quality of life

Health-related quality of life (HRQoL) is a multidimensional construct. It typically assesses the social, psychological and physical dimensions of health. HRQoL measures the patient's perception of the impact of an illness and its treatment on these domains and overall well-being. It has been considered that the measurement of HRQoL is important, because it directly reflects the patient's view on the effect of an illness on his/her well-being, and not that of a health care professional. With the help of HRQoL, we seek the measure the aspects of QoL that health and ideally also healthcare can influence. In general, two approaches to HRQOL measurement are available: specific instruments that focus on problems associated with single disease states, patient groups, and areas of function or individuals, and generic instruments that provide a summary of the health-related quality of life (Guyatt et al., 1993).

However, there are also some limitations when measuring HRQoL in EDs. There may be problems when using HRQoL as an outcome measure, as, for example, AN patients with an extreme lack of insight may not provide accurate information (Engel et al., 2009).

2.9.1 Disease-specific instruments

Disease-specific instruments have an important role in assessing the effectiveness of treatment, since generic instruments may lack sensitivity to important differences in health status that are essential for particular diseases.

In recent years, disease-specific HRQoL instruments have been developed for eating disorders. There are instruments such as the Eating Disorders Quality of Life Instrument (EDQOL) (Engel et al., 2006), the Eating Disorders Quality of Life Scale (EDQLS) (Adair et al., 2007) and the Health-Related Quality of Life in Eating Disorders Questionnaire (HeRQoLEDv2),(Las Hayas et al., 2006) .

Few of the HRQoL studies in the ED field have used both generic and disease-specific measures. In these studies, the disease-specific measures have been more informative when trying to assess HRQoL in patients with EDs. These studies have also suggested that disease-specific measures provide a good indication of an improved quality of life on follow-up (Ackard et al., 2014). In one study, it was found that disease-specific HRQoL measures are important to use when comparing HRQoL in ED patients across treatments and outcomes, and these measures may have a greater sensitivity to detect meaningful differences in the diagnosis than generic instruments (Ackard et al., 2014).

2.9.2 Generic instruments

Generic instruments can be used for different patient groups independent of the underlying disability or disease. Well-known generic instruments include the Medical Outcomes Study, 36-item short form (SF-36) (Ware et al., 1993), the Nottingham Health Profile (Hunt et al., 1981), and the 15D (Sintonen, 2001). Generic instruments can be methodologically classified into profile and single index score measures. An example of a profile instrument is the SF-36, which describes the health state from the standpoint of various physical and emotional dimensions,

e.g. bodily pain and social function. A single index score instrument (e.g. 15D) produces a single index score on a 0–1 scale. This is a necessary requirement for the calculation of quality-adjusted life years (QALYs).

2.9.2.1 15D instrument

The 15D is a generic, 15-dimensional, standardized, self-administered HRQoL instrument that can be used both as a profile and a single index score measure. The dimensions used in the 15D are moving, seeing, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity.

In the development of the 15-D generic HRQoL instrument, there have been many objectives. The first has been to evaluate the effectiveness and efficiency (cost-effectiveness/utility) of different health care programmes and technologies within disease categories in clinical trials or in average practice and across disease categories, and to thereby facilitate resource allocation decisions at the level of both clinical and health care policy. The second aim in population studies has been to describe and quantify the HRQoL of population groups and whole populations cross-sectionally and changes in the HRQoL over time (e.g. to assess the need for and effect of resource reallocation between regions). The third objective has been to assist and improve clinical practice and individual clinical decisions by pinpointing problems that need attention and to assess the clinical outcomes. Finally, the aim has been to describe the patient mix of various health care units (such as hospitals and health centres) and to standardise it when analysing and comparing the productivity of the units (Sintonen, 1994).

There have been several studies measuring HRQoL with the 15D. For example, it has been used for measuring HRQoL in several chronic conditions in the community, e.g. in pulmonary disorders, cardiovascular disorders, musculoskeletal disorders, hearing problems and psychiatric disorders (Saarni et al., 2006). Furthermore, several studies have measured HRQoL when assessing cost-effectiveness in secondary health care, e.g. in hip or knee replacement surgery (Räsänen et al., 2007), routine cataract surgery (Räsänen et al., 2006b) and routine neurosurgical spinal surgery (Räsänen et al., 2006a), but no studies to our knowledge have measured the HRQoL of ED patients using the 15D.

Table 3. Major cross-sectional studies on the HRQoL of AN or/and BN patients (AN = anorexia nervosa, BN = bulimia nervosa, EDNOS = eating disorder not otherwise specified, BED = binge eating disorder, NHP = Nottingham Health Profile, SF-36= Medical Outcomes Short-Form questionnaire, 36-item short form, EDQOL = Eating Disorders Quality of Life Instrument, WHOQoL-Bref = Abbreviated World Health Organization Quality of Life Questionnaire, QOL = quality of life, EAT-40 = Eating attitude test, PCS = correlated physical health, MCS = correlated mental health)

Study	N Diagnosis Female (%)	Mean age (years)	Quality of life measure	Recruitment Outpatient/ inpatient	Control or reference	Outcome
Keilen et al 1994, UK	52 AN 74 BN (100)	n/a	NHP	New referrals to ED treatment , n/a	Patients with somatic conditions and students	ED patients QoL worse than control group and lower than same than in e.g. coronary artery disease on domains related to emotional reactions, social isolation e.g.
Padierna et al 2000, Spain	116 AN 64 BN 17 BED (98)	23.4	SF-36	Outpatients of ED clinic	Scoring of General population	ED patients QoL worse than control, and QoL associated with severity of EAT-40
Gonzales-Pinto et al 2004, Spain	47AN (82.7)	20	SF-36	ED outpatient center	No control	Predictive values for pcs: poor outcome in previous year, comorbidity and female; for mcs: comorbidity and purging
Mond et al 2005, Australia	19 ANR 15 ANP 40 BN 10 BED n/a	ANR19 ANP25 BN 23 BED34	SF-36, WHOQOL-BREF	Patients referred to ED treatment, outpatients	Female general population	ED patients had lower Qol and the subgroup of restrictive AN had better QoL than other eating disorder patients
De la Rie et al 2005, Netherlands	44AN (100) 41BN (95.3) 68EDNOS (96.7)	26.3 29.0 29.4	SF-36	ED patients and advertisemet n/a	General population and mood disorder patients	the QOL of ED patients QoL worse than normal reference group and worse than the QOL of patients with mood disorder
Engel et al, 2006, United States	155 ED (100)	22	EDQOL	Recruited sample of students n/a	Non-ED subjects	ED patients had greater impairment in EDQOL than non-ED
Latner et al 2008, New Zealand	11AN 5BN 3BN 30EDNOS (100)	26	SF-36	ED outpatient center	General female population	ED patients had lower MCS. Qol general and PCS predicted by subjected bulimic episodes
Bamford and Sly, 2010, UK	80AN 40BN 36EDNOS (95)	26.7	EDQOL	In-and outpatients	Comparison across groups	AN<BN and EDNOS on psychological and physical/cognitive domains
Baiano et al 2014, Italy	33AN 26BN 7 BED 14EDNOS (100)	28	WHOQoL-BREF	ED patients referred to ED clinic In-and outpatients	Comparison across groups	No difference in ED groups

Table 4. Major HRQoL studies on AN and/or BN with a follow-up.
(AN = anorexia nervosa, BN = bulimia nervosa, EDNOS = eating disorder not otherwise specified, BED = binge eating disorder, NHP= Nottingham Health Profile, SF-36 = Medical Outcomes Study 36-item short form, HeRQoLED = Health-Related Quality of Life for Eating Disorders, Qol ED = Quality of Life for Eating Disorders, EEE-C = eating and exercise examination score, EDQOL= Eating Disorders Quality of Life Instrument, QOL = Quality of life, EAT-40 = Eating attitude test, PCS = correlated physical health, MCS = correlated mental health)

Study	N and Diagnosis, Female (%)	Quality of life measures	Recruitment, Mean age (years)	Control or reference	Duration of follow-up	Outcome
Padierna et al 2002, Spain,	131AN or BN, (98.5)	SF-36	Outpatients of ED clinic, 22.3	General populatio n	24 months	Significant improvement during follow-up in QoL and clinical outcome measures
Abraham et al 2006, Australia,	71 AN 55 BN 80 EDNOS n/a	EEE-C QOL scores SF-12	In-patient in ED center, n/a	Subjects without diagnosis	Baselined ischarge and 12 month follow-up	Qol improved during inpatient treatment and between admission and 12 months after discharge ED patients had lower QoL than reference population.
McHugh, 2007, USA	65 AN (100)	SF-36	AN patients entering a specialist inpatient care, 16.0	Comparis on with high and low readiness for change	Baseline and discharge (LOS 34 or 59 days)	QoL less than normal population. 81% discharged below average QoL
Munoz et al 2009, Spain	61 AN 47 BN 245EDNO S (96.6)	SF-36 HeRQoL ED	Patients entering outpatient treatment , 26.8	General populatio n	12 months	ED patients had lower QoL. After 1 year improvements in PCS
Adair et al 2010, Canada	56AN 39BN 35EDNOS (98.5)	EDQLS Quality of life inventory SF-12	ED treatment program, inpatient or outpatient, 25.6	QoL measures in different time points	3 and 6 months	EDQOL scores improved in 3 and 6 months

2.10 Prognostic factors in eating disorders

Understanding the factors that predict a favourable outcome following specialist treatment for an eating disorder may assist in improving treatment efficacy and in developing novel interventions.

A literature review identified many factors that may predict the treatment outcome. In AN, factors associated with a poor prognosis are premorbid psychiatric symptoms, e.g. depression (Keski-Rahkonen et al., 2014), rapid weight loss, bulimia nervosa, comorbid obsessive-compulsive disorder (OCD), vomiting and purging (Berkman et al., 2007; Steinhausen et al., 2002; Keski-Rahkonen et al., 2014). A favourable prognosis is associated with an early age at onset, short duration of illness, short treatment duration, a supportive relationship with the parents and a high socioeconomic status (Steinhausen et al., 2002; Berkman et al., 2007).

In bulimia, there has for most prognostic factors only been conflicting evidence (Steinhausen et al., 2009), but some studies have demonstrated that a young age of onset of BN and treatment are associated with favourable outcomes (Keel and Mitchell, 1997; Quadflieg and Fichter, 2003; Steinhausen et al., 2009).

In a recent meta-analysis, early symptom improvement in AN was revealed as a significant predictor of the outcome (Vall and Wade, 2015). In AN, results indicated that patients who had a higher weight on discharge had better outcomes on follow up. The authors suggested that ensuring that patients with severe pathology are not discharged from treatment before they have reached a satisfactory level of improvement may assist in achieving a better long-term outcome (Vall and Wade, 2015).

2.10.1 Health-related quality of life and prognostic factors

Eating disorder patients suffer from an impaired quality of life, and even after treatment the HRQoL of ED patients is lower than that of the normal population (Padierna et al., 2000). However, there is limited information on the prognostic factors that may predict the treatment

outcome measured with HRQoL. To our knowledge, no studies have sought to determine prognostic factors of HRQoL in eating disorders. .

2.11 Economic evaluation in eating disorders

Increasing attention has been paid to the health care economics of eating disorders (Crow and Peterson, 2003). It has been considered in the literature that the treatment of EDs is expensive (Stuhdreher, et al. 2012). Consequently, some health insurance providers have limited the amount of treatment provided for EDs (Crow and Nyman, 2004). Health economic studies on the treatment of eating disorders have indicated that the costs of treating AN and BN are comparable to the treatment of schizophrenia. By comparison, costs for the treatment of AN and BN were significantly higher than those for the treatment of OCD (Striegel-Moore et al., 2000).

Studies have demonstrated that the utilization of general health by care eating disorder patients is high (Mitchell et al., 2009). There is also a growing interest in studying the public health costs associated with eating disorders.

Illness-associated costs are a major concern in EDs, and in recent years, several studies have investigated these costs. These have included studies examining the national costs of ED, the third-party payer costs for ED treatment, societal costs of ED, and cost-effectiveness analysis of specific treatments. A number of further cost effectiveness analyses are planned, for instance concerning ED prevention costs (Crow, 2014).

Despite the interest in studying the costs of EDs, information regarding health care utilization, the costs of treatment and the cost-effectiveness of different treatments is still sparse (Stuhdreher et al., 2012). Knowledge of the cost-effectiveness and cost-utility of EDs is limited, and it its considered that this area will be a fertile one for continued study (Crow, 2014).

2.11.1 Treatment-related costs

2.11.1.1 Cost-of-illness studies

Cost-of-illness studies (COIs) are the most recommended instruments to assess the economic burden associated with EDs (Stuhldreher et al., 2012). COIs inform decision makers about the economic impact of certain diseases by providing a comprehensive assessment of the costs. The costs generally differ according to the perspective from which they are evaluated. These perspectives are typically the third-party payer or society. Direct costs include all medical costs. In the societal perspective, indirect costs are also incorporated (losses of productivity: reduced productivity, sickness absence, premature death) (Stuhdreher et al., 2012).

Direct costs in AN were compared in a systematic review by Stuhldreher et al. (2012). They inflated the costs to 2008 US$ using country-specific gross domestic product inflators and converted the figures to purchasing power parities (PPP). PPP account for differences in price levels between countries.

The analysis revealed substantial differences between the reviewed studies. In a study by Striegel-Moore et al. (2000), the disease-specific cost in AN was highest (US$8042 PPP in women, US$3653 PPP in men), but Krauth and colleagues (2002) calculated a considerably lower disease-specific cost of US$2291 PPP. The lowest excess costs (US$1288 PPP) were reported by Mitchell and colleagues (2009).

In BN, the direct costs have been more homogeneous, with reports of US$5016 PPP (Mitchell et al., 2009) and US$3941 PPP (Striegel-Moore et al., 2000) in women and US$5169 PPP in men. Krauth and colleagues (2002) reported low direct costs for BN of US$127 PPP.

In BED, reported direct costs have been US$3487 PPP (Dickerson et al., 2010) and US$2214 PPP (Grenon et al., 2010). Reported costs for EDNOS have almost been the same as in BN: US$5301 PPP (Mitchell et al., 2009) and US$4267 PPP (Striegel-Moore et al., 2000).

When comparing different economic analyses, there are several reasons for uncertainty. For example, most economic analyses have been clinical trials not representing the average ED patient, economic estimates have been inaccurate, sample sizes have been too small, and patient data have often been incomplete (Table 5). In a review on costs and cost-effectiveness, the methodological quality of studies was found to be heterogeneous, and most of the studies did not meet the criteria for a cost-of-illness study (Stuhldreher et al., 2012). The authors only included three cost-of-illness studies on AN or BN.

Table 5. Major studies describing the healthcare costs for anorexia and bulimia nervosa. There are several differences in the design and analysis of these studies, which reduces the comparability of the cost data.
(AN= anorexia nervosa, BN = bulimia nervosa, EDNOS = eating disorder not otherwise specified, BED = binge-eating disorder, BMI = body mass index, OCD = obsessive-compulsive disorder, CBT = cognitive-behavioural therapy)

Study	Perspective	Country	N and diagnosis	Duration of the follow-up	Costs	Description	Main findings
O´Brien, Patrick, 1998	Third party Payer	USA	AN=641 BN=326	Duration of inpatient stay AN=13 days BN=days	Inpatient cost AN= 12 390 $ BN= 9120 $	Inpatient cost estimates, adjusted for medical inflation and cost-to-charge ratios were developed using data from all-payer discharge database	Cost of acute hospitalization for AN and BN was estimated
Krauth et al 2002	Society	Germany	Estimation of cases of AN=4600 and BN=590 in inpatient treatment per year	Estimation of total costs for society and annual cost per AN and BN	Inpatient, health insurance, rehabilitation pension insurance, inability to work. Cost of illness app 195 million euros, bulimia 124 million.€ in Germany. Annual cost per AN 5300€, bulimia 1300€.	Cost-estimates were projections derived from benefit data, pension insurance and from epidemiological studies (prevalence, mortality). Authors estimated the average cost of treating AN including indirect costs (inability to work, mortality)	This study underlines the significance of indirect costs due to premature death, but also highlights the extremely cost-intensive treatment. The hospitalixation cost per AN (12,800€)patient is markedly higher than the average hospitalization cost (3600€)
Striegel-Moore et al 2000	Third party payer	Usa	AN= 517(Female) 49 (Male) BN= 725 (Female) 41(Male) EDNOS= 756 (Female) 176 (Male)	One year	One year data from national insurance database from claims from ED patients and other patiets	Treatment of AN or BN was comparable in cost of treatment of schizophrenia. ED costs were more than in the treatment of OCD	Striegel- Moore et al 2000
Mitchell et al 2009	Third party Payer	USA	ED diagnosis= 167	52,5 months	Hospital care, healthcare provider, prescription medication AN 3405 $ BN6639 $ EDNOS 6887$ (Group1)	Health insurance database	Health care costs remained elevated after a diagnosis of an ED for an extended period of time
Haas et al 2012a	Costs of the hospitalization	Germany	AN=101 BN=95	The length of Inpatient stay during 2006-2009	Inpatient cost using micro-costing AN= 5251€ BN=3265€	The aim of the study was to analyze if psychosomatic inpatients treated for eating disorders could be reinbursed by a common per diem rate	The diagnosis of AN predicted higher costs. Predictors of high costs were found.
Crow, Nyman 2004	Third party Payer	USA	AN	Cost-modelling analysis was used to estimate the incremental cost-effectiveness of AN treatment	Adequate care(inpatient, partial hospitalization, outpatient psychotherapy, medication) and Usual care (limited intensity)	Adequate care=$119200 Usual care= 36200 $ Adequate care model yeald a cost per year of life saved of only $30000	The comprehensive treatment of An appears to be quite cost-effective in terms of cost per year life saved.
Byford et al 2007	Third party Payer	UK	AN inpatient n=47 specialist out-patient n=45 general out-patient n=43	2 years	service-providing perspective: health, social services, education, voluntary and private sectors.	Inpatients 34531 £ Outpatient sp 26 738 £ General 40 791£	There were no significant differences in clinical outcomes between groups, but specialists out-patient was less costly than inpatient and general out-patient treatment

Lock et al 2008	Third party payer	USA	AN	39,686$	Medical hospital, outpatient family therapy, medication , doctor visit	Based on clinical records, the costs and effects of outpatient family therapy were evaluated	Most of the costs associated with outcome were secondary to medical hospitalization. Adolescent treatment costs appeared to be lower when families are used effectively to aid in treatment.
Haas et al 2012b	Costs of the hospitalization	Germany	AN=127	Patient treated from 1/2005 to 3/2009. Mean lenght of hospitalization (LOS)28 days	Cost calculated based from actual consumption of resources by each patient 4,647€/6831U$	The aim was to calculate inpatient costs for average AN patient and to identify significant predictors of cost.	BMI predicted inpatient costs per day, also comorbidity did increase costs.
Toulany et al 2015	Costs of the hospitalization and caregiver perspective	Canada	AN=73	Inpatient stay during 2 years	Inpatient cost= 51 349 Can $ Total societal cost = 54 932 Can $	Micro-costing of cohort study involving adolescent patients admitted for treatment of anorexia nervosa at a tertiary care. Hospital costs and caregiver costs were determined	Economic burden of inpatient treatment for adolescents with AN on hospitals and caregivers is substantial. Lower BMI increased the costs.

Stuhldreher et al 2015	Third party Payer	Germany	AN=242	3 months	Direct costs (costs of the treatment) and indirect costs(disability) Mean cost for 3-month was €5866, direct costs were 57%	To estimate direct and indirect costs of AN and to identify cost determinant	Mean cost driver was hospitalization
Koran et al 1995	Third party Payer	USA	BN=71	Costs during 32 weeks	Costs were calculated by multiplying clinics professional fees by the number of visits and addid medication costs	Cost-effectiveness of CBT vs desipramine and combination	Medication appeared to be more cost-effective than CBT but the authors discuss the pitfalls and limitations of this study
Crow et al 2009	Society	USA	BN=128	Costs during 12 months	Costs of treatment and travel time for therapists and subjects. Unit costs were derived from the Medicare website,	Aim was to compare face-to face CBT ($9324) vs telemedicine CBT ($7300)	Telemedicine and face-to –face CBT were similarily effective and costs in telemedicine substantially less underlining the usefulness of telemedicine in this treatment.
Crow et al 2013	Third party Payer	USA	BN=293	Costs during treatment 4 months	Inpatient costs, outpatient and emergency room utilization and medication costs	Aim was to analyze the costs of stepped care ($ 12146)vs CBT($ 20317)	Stepped care appeared more cost effective than CBT

2.11.1.2 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is applied to compare at least two alternative treatments regarding costs and outcomes. Using an incremental analysis (differences in costs are put in relation to differences in effects), they combine both parameters to determine the most efficient treatment. CEAs support the decision on how to allocate scarce resources in healthcare systems. CEAs can be conducted within clinical trials.

2.11.1.3 Cost-effectiveness analysis in BN

Crow et al. (2013) reported a cost-effectiveness analysis of a randomized controlled trial for BN treatment. BN patients were randomized into either a cognitive behavioural therapy treatment, potentially augmented by fluoxetine, or stepped care treatment (treatment beginning with guided self-help, then fluoxetine, then CBT). To account for uncertainty, cost-effectiveness ratios were examined with boot strapping and sensitivity analyses. According the study, the stepped care approach was both more effective and less costly. The cost per abstinent participant was US$12 146, while the CBT was US$20 317. In those participants who achieved abstinence from BN symptoms, the QoL improved significantly more (Crow, 2013) (Table 5).

2.11.1.4 Cost-effectiveness analysis in AN

In the literature, there are few recent studies examining specific costs related to the treatment of EDs. Stuhldreher et al. (2015) described the results of a cost-effectiveness analysis of AN treatment outpatients. They collected health care utilization data on all participants (225 of the 242 participants). Specifically, they also examined retrospective recall of costs over the three months preceding the study. The cost in the three months preceding trial entry was €5866 (€3374 direct, €2492 indirect). The main driver of costs was hospitalization for eating disorder treatment. A cost analysis involving 127 individuals with anorexia nervosa has also been conducted by Haas and colleagues (2012). In this study, the cost of services was calculated based on resource utilization using bottom-up microcosting from a hospital perspective. The mean cost was €4647 (US$6831) per case. The presence of psychiatric comorbidity and lower admission of BMI were predictive of a higher overall cost (Table 5).

2.11.1.5 Cost-effectiveness of prevention

A study by Wang et al. (2011) assessed the economic effect of the school-based obesity prevention programme Planet Health for preventing disordered weight control behaviours and determined the cost-effectiveness of the intervention. They estimated that with the help of the programme, one case of bulimia nervosa would have been prevented, indicating $33 999 in medical costs and 0.7 QALYs saved.

2.11.2 Quality-adjusted life year as an outcome measure

The quality-adjusted life year (QALY) is a metric that combines mortality and morbidity into a single index score. QALYs offer a broad definition of a successful medical care and treatment outcome (Jennet 1992). Cost-utility analysis is a type of cost-effectiveness analysis that examines the costs and effectiveness of therapies by using the calculation of cost per quality-adjusted life year (QALY) as a unit of effectiveness. Cost-utility analysis is considered the gold standard both for reporting cost-effectiveness results in the literature and for informing policy decisions on the allocation of health care resources (Pirraglia et al., 2004).

Many studies regarding eating disorders have focused on weight and eating behaviours, which may fail to capture the disability caused by the illness (Keilen et al., 1994). QALYs can be used in comparing different diseases and treatments (Keilen et al., 1994). Counting of the cost per QALY is based on QoL scores, statistical life expectancy and the costs of the treatment.

Very few studies have used QALYs as an outcome measure in eating disorders, although it is recommended in the literature to measure the cost per QALY (Stuhdreher et al., 2012).
In a study by Lynch et al. (2010), a QALY was estimated for treating recurrent binge-eating disorder treatment. They compared one group receiving standard care with another group receiving both standard care and CBT group therapy. The latter was more expensive but produced more binge-free days, and the cost per QALY was $26 847 (Lynch et al., 2010).

2.12 Summary of the reviewed literature

BN and AN are serious medical conditions that usually start in young adolescence and mainly affect women. The prevalence of BN is estimated to range from 0.9 to 2.9% in women and from 0.1 to 0.5% in men. The prevalence of AN in women varies from 0.3 to 2.2%, while in men the prevalence of AN was estimated to be 0.24%. AN and BN result in high mortality and have a major impact on the health-related quality of life (HRQoL) of the sufferers. In a meta-analysis, SRM was 1.93 in BN and 5.86 in AN, being one of the highest in the field of psychiatry (Arcelus et al., 2011). BN and AN are heritable, but the aetiology of eating disorders is considered to be multifactorial (Cooper and Steere, 1995). Whether a person develops an eating disorder depends on individual vulnerability, consequent on the presence of biological or other predisposing factors, their exposure to particular provoking risk factors (Jacobi et al., 2004) and on the operation of protective factors (NICE Guideline, 2004).

The HRQoL of eating disorder patients has been poor, and even after treatment the HRQoL is less than that in the normal population. The costs of ED treatment have been considered high. No previous studies on eating disorders have measured the cost per QALY. The prognostic factors regarding HRQoL are unclear, and the long-term HRQoL of ED patients is undetermined.

3 AIMS OF THE STUDY

The aims of this study were to measure the cost-effectiveness of treatment in terms of quality-adjusted life years (QALYS) in BN and AN, to assess the prognostic factors in AN and to measure the long-term HRQoL in BN and AN.

The specific aims were as follows:

1) and 2) To investigate HRQoL and cost-effectiveness in terms of quality-adjusted life years (cost per QALY) in bulimia nervosa and anorexia nervosa treatment in a naturalistic treatment setting. (Studies I, II)

3) To assess the prognostic factors related to HRQoL in AN using a novel Bayesian method in patients treated at the Eating Disorder Unit. (Study III)

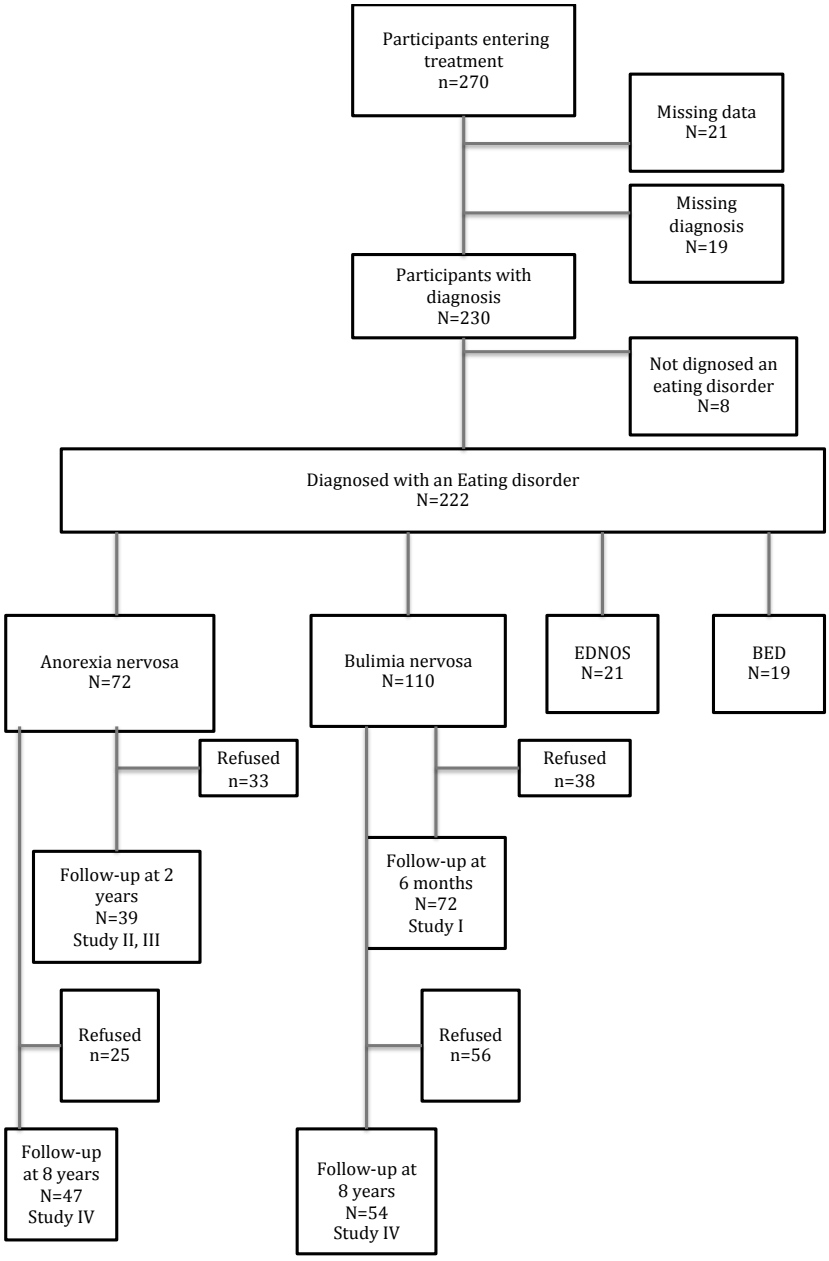
4) To measure the long-term quality of life of anorexia nervosa and bulimia nervosa patients after approximately 8 years from the start of treatment. (Study IV)

4 MATERIALS AND METHODS

4.1 Study design and participants

The subjects of this naturalistic follow-up study comprised of 72 consecutive patients diagnosed with AN and 110 patients diagnosed with BN entering treatment in the Eating Disorder Unit of Helsinki University Central Hospital from June 2002 to December 2003. The number of binge-eating disorder (BED) (n = 19) and eating disorder not otherwise specified (EDNOS) (n = 21) patients was so limited that they were not analysed in this study. The HRQoL of ED patients at baseline was compared with that of a representative sample of the general female population studied in the National Health 2000 Health Examination Survey (Aromaa et al., 2004). For comparison, the population sample was weighted to correspond to the age distribution of the patients.

Figure 1. The flow-chart of the study design



The diagnosis of AN and BN was based on clinical assessment (International Statistical Classification of Diseases and Related Health Problems ICD-10 criteria) by a psychiatric consultant or resident. The inclusion criterion was an ED diagnosis, and no exclusion criteria were introduced.

At baseline, the subjects completed the 15D HRQoL questionnaire (http://www.15d-instrument.net/15d, Sintonen, 2001) and the Eating Disorder Inventory (EDI) questionnaire (Garner et al., 1983), as well as a specific questionnaire developed for the needs of this study enquiring, for example, about the patients' self-perceived health status and eating habits. Follow-up questionnaires were mailed to all subjects who had returned the first questionnaire. The follow-up questionnaires were mailed approximately six months, two years and eight years after the start of treatment at the Eating Disorder Unit. A reminder was sent if the participant did not respond to the first questionnaire mailing.

The study protocol was approved by the Ethics Committee of Helsinki University Central Hospital, Finland.

Table 6. Baseline characteristics of the bulimia nervosa and anorexia nervosa participants (with SDs) (BN = bulimia nervosa, AN = anorexia nervosa, EDI = Eating Disorder Inventory (the higher the score, the greater the eating disorder problems), BMI = body mass index, HRQoL score = health-related quality of life score

Variable	Bulimia Nervosa 6 months follow-up (n=72)	Bulimia Nervosa 8 years follow-up (n=54)
Mean Age, (SD)	25(6.0)	25.7(6.0)
Age range	(17-48)	(17-45)
Female %	100	100
HRQoL score	0.80 (0.09)	0.818 (0.088)
EDI score	80 (28)	82 (32)
BMI kg/m2	22 (3.9)	21(7.3)

Variable	Anorexia nervosa 2 years follow-up (n=39)	Anorexia Nervosa 8 years follow-up (n=47)
Mean Age, (SD)	22(5.0)	23(7.8)
Age range	(17-42)	(17-64)
Female %	100	100
HRQoL score	0.792 (0.12)	0.807 (0.123)
EDI score	73(27)	74 (29)
BMI kg/m2	16.5 (2.2)	16.4(2.1)

4.1.1 Drop-outs

Only approximately half of the patients responded to the follow-up and data were also missing from completed questionnaires. However, the patients were approached before the treatment even started, and many of the patients may have decided not to begin the treatment, since ED patients are usually very ambivalent about receiving treatment, and dropout rates from inpatient treatment for eating disorders are very high (Pham-Scottez et al., 2012). The representativeness of the present study group was tested in terms of age, HRQoL, BMI and EDI, and they did not differ from those individuals who did not respond to the follow-up.

4.1.2 Follow-up in bulimia nervosa

For participants diagnosed with BN who returned the first questionnaire (n = 110), the follow-up questionnaires were mailed after 6 months and approximately after 8 years from the start of treatment. Seventy-two BN patients (62%) returned the follow-up questionnaire at 6 months, and at 8 years, fifty-four patients (49%) responded and were thus available for analysis. Those who did not return the questionnaires did not differ statistically significantly regarding HRQoL or age compared to the responders (mean age 25.7 (SD 5.9) vs. 25.6 (SD 6. 8), p = 0.937; mean 15D score 0.818 (SD 0.09) vs. 0.815 (SD 0.94), p = 0.861).

4.1.3 Follow-up in anorexia nervosa

Those who were diagnosed with AN and who returned the first questionnaire (n = 72) were mailed the follow-up questionnaires 2 years and 8 years following the start of treatment. At the 2-year follow-up, thirty-nine patients returned the questionnaire (53%), while at the 8-year follow-up, forty-seven AN patients (65%) returned the questionnaire. Those who returned only the baseline questionnaire did not differ significantly regarding age or HRQoL from those who also returned the 2-year or 8-year questionnaire (mean age 23.3 (SD 7.8) vs. 22.5 (SD 5.9), p = 0.682; mean 15D score 0.807 (SD 0.12) vs. 0.823 (SD 0.10), p = 0.565).

4.2 Clinical assessment

Patients were examined by a psychiatric resident or consultant when entering the Eating Disorder Unit. If needed, consultation with an internist and dietician was provided. After the consultations, interventions were adjusted to each patient's needs by a multidisciplinary team.

4.3 Treatment interventions

The Eating Disorder Unit provides tertiary-care-level treatment. The Unit is part of Helsinki University Central Hospital and provides specialized assessment and treatment of adults with EDs within a catchment area of approximately 1.5 million people. Some tertiary referrals for inpatient treatment are also taken from other parts of Finland. Most treatment is provided at the outpatient level, but day patient treatment and inpatient wards are also available. The Eating Disorder Unit uses a cognitive-behavioural approach in the treatment. The treatment interventions during this study followed normal hospital procedures. When this study began, it was the first specialized ED Unit in Finland.

4.3.1 Treatment interventions in bulimia nervosa

In the Eating Disorder Unit, the treatment of BN patients followed the stepped-care programme. First, the patients received psychoeducational lectures including elements of cognitive behaviour therapy. Experienced dieticians and internists gave the lectures. After these, patients who still suffered symptoms were invited to cognitive-behavioural group (CBT) therapy (8 sessions). Therapy sessions were held by an experienced dietician and a psychiatric nurse. Patients who were still symptomatic after the group therapy received individual CBT provided by a psychiatric nurse (about 20 sessions). Short-interval treatment in the day hospital or on the inpatient ward was offered if the patients were unable to stop binging and purging in outpatient care. The patients also received psychopharmacological treatment and, if needed, individual nutritional counselling and social skills training.

4.3.2 Treatment interventions in anorexia nervosa

In AN, the treatment interventions consisted of psychoeducation, cognitive-behavioural group and/or individual therapy, motivational interviews, social skills training, nutritional counselling and psychopharmacological treatment. If the body mass index (BMI) was 16 kg/m^2 or lower, inpatient treatment was recommended. After the inpatient treatment, the patients were invited to a day hospital and they started a 40-session cognitive-behavioural therapy intervention after their BMI was 17 kg/m^2 or higher.

4.4 Baseline and follow-up measurements

4.4.1 HRQoL (15D instrument)

HRQoL was assessed using the 15D questionnaire (Sintonen, 2001). The valuation system of the 15D is based on the application of multi-attribute utility theory. A set of preference (or utility) weights, elicited from the general public through a three-stage valuation procedure, is used in an additive aggregation formula to generate the utility score (15D score, a single index number) over all dimensions (Sintonen, 1994a, 1995). The maximum score is 1 (indicating no problems in any dimension) and the minimum score 0 (being dead). The minimally important difference or change in the 15D score is 0.03, indicating clinical significance (Sintonen, 1994b; Alanne, 2015). In most of the important properties (reliability, content validity, discriminatory power and responsiveness to change), the 15D compares favourably with other similar HRQoL instruments (Stavem, 1999; Hawthorne, et al. 2001; Moock and Kohlman, 2008; Vainiola et al., 2010).

4.4.1.1 Age-adjusted comparison group from the female general population

The HRQoL of ED patients at baseline was compared with that of a representative sample of the general female population studied in the National Health 2000 Health Examination Survey

(Aromaa et al., 2004). For comparison, the population sample was weighted to correspond to the age distribution of the patients.

4.4.2 Clinical outcome measures

4.4.2.1 Eating Disorder Inventory

The clinical outcome was measured using the Eating Disorder Inventory (EDI) (Gardner et al., 1983; Welch et al., 1990), and based on the self-reported weight and height, BMI was calculated accordingly. The Eating disorder Inventory (EDI) (Garner et al., 1983) is a one of the most widely used self-report inventories for eating disorders. The EDI is designed to assess the psychological characteristics of AN and BN (Garner et al., 1983). It has repeatedly been shown to be a reliable and valid instrument (Garner et al., 1983; Welch et al., 1990). The EDI is comprised of 64 items divided into eight subscales. These subscales are Drive for Thinness, Perfectionism, Bulimia, Body Dissatisfaction, Interpersonal Distrust, Ineffectiveness, Interoceptive Awareness and Maturity Fears. In the EDI, there is a recognized cut-off for the total score of 42, above which respondents are regarded as being susceptible to a clinical eating disorder (Bennett and Stevens, 1997). According to preliminary data, the total initial EDI score is associated with a poor prognosis in AN patients (Bizeul, 2001).

ED patients self-report their current weight in the EDI. Eating disorder patients have been extremely accurate in self-reporting their weight, although AN patients slightly over-report their weight (McCabe et al., 2001). In the Eating Disorder Unit, where this study was carried out, a cut-off for each subscale of the EDI is in clinical use. This cut-off is 5 points, except for the subscale "Perfectionism", for which the cut-off of 10 is used. The cut-off of the EDI (<46) represents the cut-offs of all the eight subscales combined, indicating an improvement in the psychological characteristics of EDs.

4.4.2.2 Questionnaire developed for the needs of the study

A specific questionnaire developed for the needs of this study was also used. It assessed the self-reported health status of the patients and included questions about the eating habits, for example: "I control my eating" (scale 0–5: never, rarely, sometimes, quite often, always) or "I avoid eating".

4.5 Cost-utility

Since 2002, HRQoL data have been collected on approximately 15 000 patients in approximately 20 different specialties before and after interventions performed at the hospitals of the Helsinki and Uusimaa Hospital District (Räsänen et al., 2005). The observed change in HRQoL is related to routinely collected cost data on specialist medical care provided to the patients in order to determine the cost-utility of these interventions. These results enable the comparison of the every-day cost-utility of a range of interventions. These results also offer decision-makers relevant information for the planning of future specialist healthcare services.

4.5.1 Costs of the treatment

The direct hospital costs of the treatment were obtained from the Ecomed® clinical patient administration system (Datawell Ltd., Espoo, Finland). All cost data concerning the treatment of individual patients in the Eating Disorder Unit are stored in this database. All speciality-relevant costs at the Eating Disorder Unit (interventions, ward, ambulatory visits, laboratory and radiology) cover the period from the start of treatment to the end of the 6-month (BN) and two-year (AN) follow-up. The costs are based on current prices in 2002–2005. We did not include productivity loss due to potential work disability or other non-healthcare costs. Medication costs during inpatient treatment are included in the costs, but other medication costs are not.

4.5.2 Cost-utility in bulimia nervosa

BN patients often can have relapsing course and many of the patients do not receive any treatment. We analysed two scenarios based on different sets of assumptions about the development of health outcomes when treated or not treated.

4.5.2.1 Best-case analysis in BN

In the best-case sensitivity analysis (*i.e. the most optimistic scenario regarding cost-utility*), we analysed a scenario in which HRQoL would not improve without treatment. We also assumed that the HRQoL gain from the treatment by 6 months would last until the end of the remaining

statistical life expectancy of each patient. After this, we calculated the QALYs gained by the treatment accordingly. By dividing the mean cost by the mean number of QALYs gained, we obtained the cost per QALY gained (the cost-utility) (Figure 2).

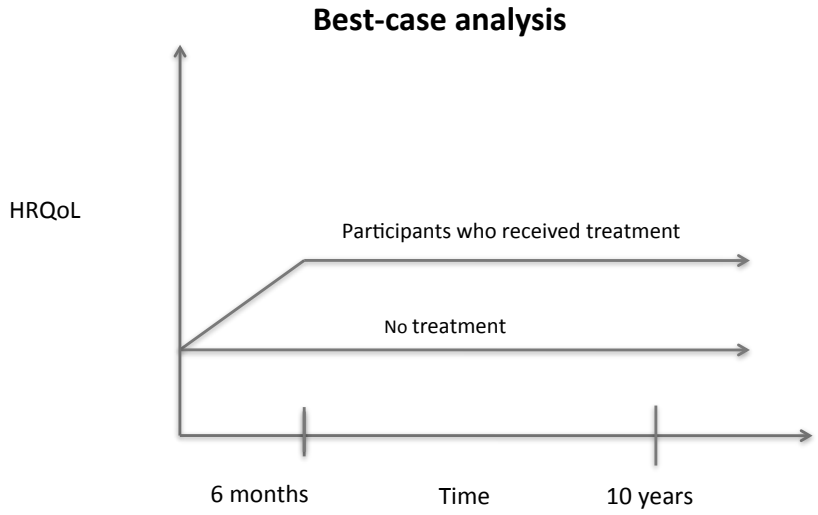


Figure 2. Best-case analysis in BN.

4.5.2.2 Base-case analysis in BN

In the base-case cost-utility analysis (i.*e. the most pessimistic assumption*), we assumed that even if the patients do not receive treatment, their HRQoL will improve linearly during 10 years to the same level as reached by the treated patients after 6 months of treatment. For those who received treatment, we assumed that the HRQoL gain by 6 months would persist until 10 years. After this, we calculated the QALYs gained by the treatment accordingly. The mean cost of the

treatment was then divided by the mean number of QALYs gained, giving the cost per QALY gained (Figure 3).

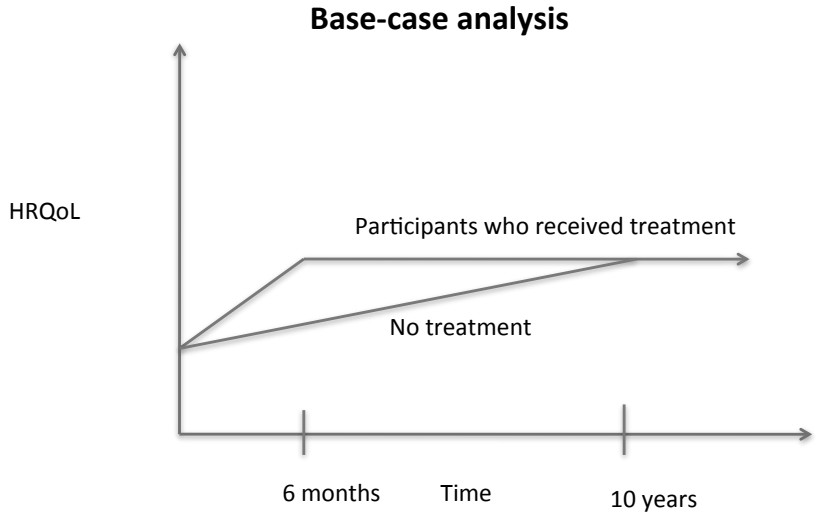


Figure 3. Base-case analysis in BN.

As the gain from treatment is expected to last many years, the cost per QALY is also reported using a discount rate of 5%, which is the typical approach used in health economics (Drummond et al., 2005).

4.5.3 Cost-utility in anorexia nervosa

The course of AN is highly variable, and we therefore analysed two scenarios based on different sets of assumptions about the development of health outcomes when treated or not treated.

4.5.3.1 Best-case analysis in AN

In the best-case sensitivity analysis, *(i.e. the most optimistic scenario regarding cost-utility),* we analysed a scenario where HRQoL would not improve without treatment. We also assumed that the HRQoL gain from the treatment by two years would last till the end of the remaining statistical life expectancy of each patient. The QALYs gained were then calculated. Dividing the mean costs of the treatment by the mean HRQoL gain gives the cost per QALY gained. This analysis assumes that the difference between treated and not-treated patients achieved during the first two years of treatment remains the same for the rest of life expectancy, but the HRQoL can improve in both groups over time (i.e. two years after start of treatment) (Figure 4).

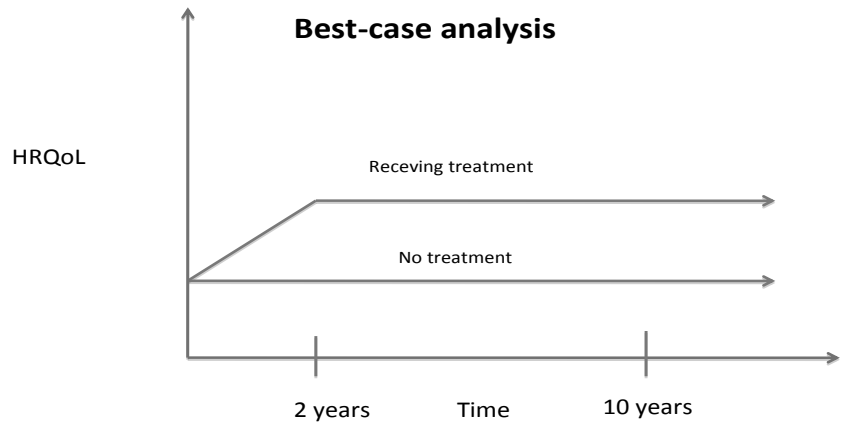


Figure 4. Best-case analysis in AN.

4.5.3.2 Base-case analysis in AN

In this analysis, we assumed that if we do not treat the patients, their HRQoL will improve linearly in 10 years to the same level as treated patients have achieved after two years from the start of the treatment (base-case cost-utility analysis *i.e., the most pessimistic scenario regarding cost-utility).* We also assumed that the HRQoL gain by two years would persist until 10 years for those treated. Dividing the mean costs by the mean HRQoL gain gives the cost per QALY gained (Figure 5).

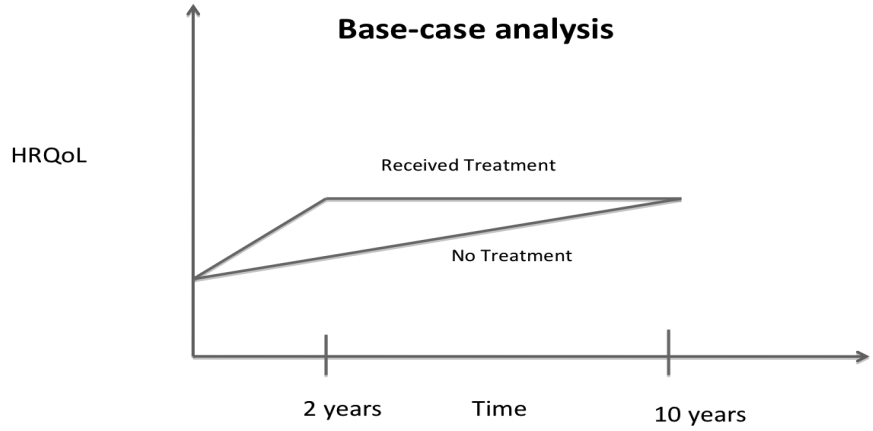


Figure 5. Base-case analysis in AN.

The cost per QALY is also reported using discount rates of 3–5%, which is the typical approach used in health economics, as the gain following treatment is expected to last many years (Drummond et al., 2005).

4.6 Statistical methods

Data were analysed using the statistical software SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). The results are presented as means and standard deviations (SDs) for continuous variables, and as percentages. The significance of differences between before and after treatment scores was analysed with the Student's two-tailed paired t-test for dependent samples, and the difference between patients and the general population with the two-tailed independent samples t-test. P-values ≤0.05 were considered statistically significant.

4.6.1 Bayesian methods

The fundamental ideas of the Bayesian statistical paradigm have existed for centuries (Bayes, 1763), but only in recent decades have Bayesian statistics been applied in psychological research (Andrews and Baguley, 2013). The core idea behind Bayesian statistics is that a posterior distribution of a particular parameter can be generated as a function of both observed data and prior knowledge (Kruschke, 2011). The Bayesian approach therefore has the advantage of permitting researchers to incorporate prior knowledge into their data analysis, in contrast to traditional frequentist statistics. The creation of 95% credible intervals is also allowed by Bayesian data analysis, indicating that the probability that a particular parameter lies within the specified interval is 95%.

Bayesian statistics are widely used in medical statistics, including clinical trials, epidemiology and meta-analyses (Ashby, 2006). One advantage of the Bayesian method is that analysis can also be performed with small data sets, with certain limitations (Blomstedt et al., 2007; Ng and Jordan, 2002; Wang et al., 2004; Greenland et al., 2000; Bellazzi and Zupan, 2008; Soini et al., 2009). In terms of prediction accuracy (Blomstedt et al., 2007; Soini et al., 2009), variable selection and multiple performance measures (Soini et al., 2009), a web-based naïve Bayesian classifier (NBC) method equalled or outperformed logistic regression, especially with small data sets. If the data set is small, dependencies are weaker and the model found to be best may not be very much better than the second best (Myllymäki et al., 2002). Bayesian analyses can use informative priors based on previous comorbidity findings (Gallagher and Brown, 2015). The Bayesian method has previously been used in psychiatry, for example in mood and anxiety disorders (Gallagher and Brown, 2015) and in schizophrenia (Samara et al., 2016).

4.6.1.1 Bayesian method in our study

In our study, we aimed to determine the factors that may predict the treatment outcome in AN. We decided to use the Bayesian method, since it is a novel method in the field of eating disorders, and in addition it can be used on small sample sizes with certain limitations.

In our study, we aimed to use the Bayesian method to investigate the prognostic factors in AN. For the analysis, we formed four outcome variables as follows:

1. A patient reaching at least 0.85 on the HRQoL index score; variable referred to as *QoL*.
2. A patient reaching a BMI of at least 19 kg/m^2; variable referred to as *BMI*
3. A patient reaching an EDI score of less than 46; variable referred to as *EDI*
4. A patient fulfilling at least two of the previous three criteria; variable referred to as *sum*.

For HRQoL, a cut-off of 0.85 was chosen on the basis that it represents the average HRQoL of psychiatric patients in Finland (Saarni et al., 2007). For BMI, a cut-off of >19 was applied to be sure that the patients had reached a normal weight, because the threshold for being underweight is BMI < 18.5 according to WHO (http://apps.who.int/bmi/index). The cut of for EDI was <46, which is in clinical use in the Eating Disorder Unit.

In this study, PREQ, a web-based naïve Bayesian classifier (NBC), was used. PREQ can use multidimensional priors, e.g. separate priors for the outcome variable in general and for the outcome variable according to each predicting variable. However, the data modelling was performed without informative *a priori* information (Ryynänen et al., XXXX). PREQ has been developed from its previous application, the B-Course tool (Myllymäki et al., 2002).

Relationships were assessed between class variables and predictors with posterior odds (PO). These equal the product of prior odds as well as the likelihood ratio, and also the estimated inversed probabilities, giving an idea of the predictor's strength. The POs were determined by

$$PO = P_{PC}/P_{NPC}$$

in which P_{PC} represents the predicted class and P_{NPC} the non-predicted class. POs are not directly dependent on the amount of data (Soini et al., 2009).

In this preliminary study, the data were unfortunately so limited that it was not possible to form separate training and test sets. We wanted to avoid overfitting the model, and a new data set (n = 30) was therefore first formed by randomly removing nine cases. This procedure was repeated four times to obtain five randomly diminished training sets. After this, NBC prediction

was performed for all four outcome variables in all five training sets. Next, only those predictor variables that were present in at least three models were then selected, thus forming a final training set containing seven potential predictor variables.

For the total data set, final modelling was performed separately for all four outcome variables by using the set of seven predictor variables. The model was considered overfitted if a model with more than three predictor variables was obtained. Overfitting was noted by obtaining unrealistic models with high accuracy (up to 100%). When this occurred, the number of predictor variables was limited to a maximum of three.

The data set was tested using leave-one-out cross-validation (LOOCV) (Soini et al., 2009), because separation of the training and test sets was not possible. In this method the learning algorithm is trained multiple times using all but one of the training set data points. The NBC tries to predict which data point is left out by using all the other training examples.

The logarithmic loss function (log score) is a way of presenting losses from actual outcomes in prediction tasks: the log score is a measure of the prediction distribution (the closer to zero, the better). The log score reaches a minimum only when true probabilities are predicted, thus being a strictly proper scoring rule. The log score also penalizes the inability to produce faithful probabilities. Due to the lack of a test set, the specificity, sensitivity, predictive values and area under the ROC curve were not relevant for calculation.

4.7 Ethical aspects

All patients received routine treatment and, besides being asked to complete the questionnaires and to give written informed consent, were not approached in any other way. The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District.

4.8 Personal involvement

The author had the main responsibility for analysing the data. She participated in the design of the study and the writing of the manuscripts. She served as the first and corresponding author of all four publications of the study.

5 RESULTS

5.1 Cost-utility in bulimia nervosa (Study I)

5.1.1 Clinical outcomes

All the BN patients (n= 72) were female, their mean age was 25 years (SD 6.0) and the average duration of illness was 8 years (SD 6.3). The mean EDI score was 80 (SD 28) and mean BMI was 22.0 kg/m^2 (SD 3.9) (Table 6). The patients suffering from BN had a global, severely impaired HRQoL compared to the age-standardized general population (0.80 vs. 0.96) (Fig. 1) at baseline. Those who only returned the baseline questionnaire did not differ significantly regarding HRQoL, age or treatment costs from those who also returned the 6-month questionnaire.

After 6 months from the start of the treatment, there was a statistically significant and clinically important improvement in the mean HRQoL score of the BN patients (0.85, $p < 0.001$) (Study I, Table 1, Figure 2), although it still remained significantly worse ($p < 0.001$) than that of the general population (Study I, Table 1). A significant improvement occurred in seven dimensions of 15D, and there was a significant decrease in the EDI score ($p < 0.001$), indicating an improvement in the psychological characteristics of bulimia. The BMI did not significantly change ($p = 0.1$).

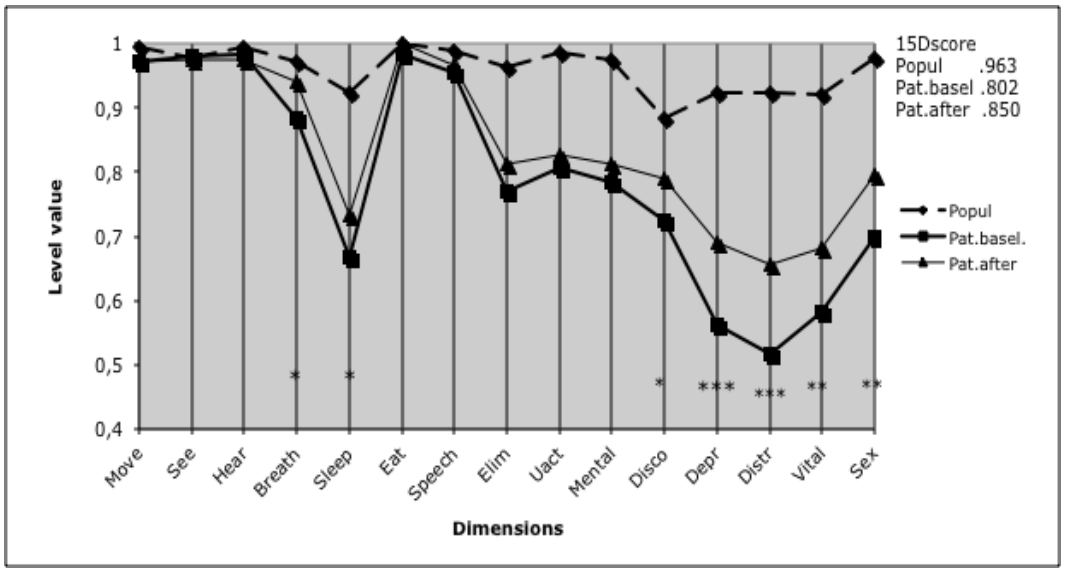


Figure 6. The 15D profiles of bulimia nervosa patients (n = 72) at baseline and after 6 months of treatment, as well as those of the age- and gender-matched general population (n = 1482) (* denotes a statistically significant improvement from baseline at the $p < 0.05$ level, ** at the $p < 0.01$ level and *** at the $p < 0.001$ level).

5.1.2 Costs

The mean cost of providing treatment during the 6-month follow-up was €3 972 ± 5 518. The mean distribution of costs is presented in Study I, Table 2.

5.1.3 Cost-utility and sensitivity analysis in bulimia nervosa.

The mean number of QALYs gained ranged from to 2.729 (best-case analysis) to 0.241 (base-case analysis), and the mean undiscounted cost per QALY gained ranged from €1455 (best-case

analysis) to €16 481 (base-case analysis) (Study I, Table 3). The corresponding discounted (5%) figures ranged from €4428 to €19 663 per to QALY gained, respectively.

5.2 Cost-utility in anorexia nervosa (Study II)

5.2.1 Clinical outcomes

All patients were female (n = 39). At baseline, the mean age was 22 years (SD 5.0), mean 15D score 0.792 (SD 0.12), mean BMI 16.5 kg/m^2 (SD 2.4) and mean EDI score 73 (SD 27) (Table 6). Those who returned only the baseline questionnaire did not differ significantly regarding HRQoL, age or treatment costs from those who also returned the 2-year questionnaire. Compared with the mean 15D score of the age-matched general female population, AN patients had a global, severe deterioration in their HRQoL at baseline (mean 15D score 0.963 vs. 0.792) (Study II, Figure 1). After 2 years from the start of the treatment, there was a significant improvement in 8 of the 15 dimensions, and the improvement in the mean 15D score (0.855 at two years) was statistically significant and clinically important (MID > 0.03) ($p < 0.001$) (Figure 3). The BMI increased in a statistically significant manner from 16.6 to 18.4 kg/m^2 ($p < 0.001$) after 2 years from the start of treatment. There was also a significant improvement in the EDI score ($p < 0.001$), indicating an improvement in the psychological characteristics of AN. Although the HRQoL of AN patients had improved during the follow-up, after two years from the start of the treatment the HRQoL still remained significantly worse in AN patients ($p < 0.001$) than in the age-matched general population (Study II, Figure 1).

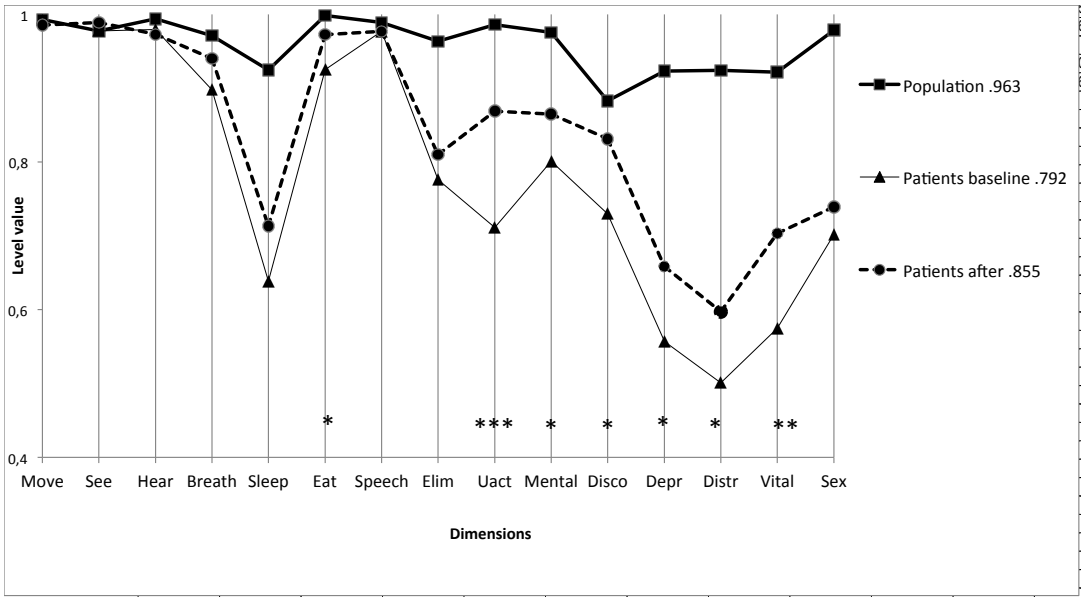


Figure 7. The 15D profile of anorexia nervosa patients (n = 39) at baseline and after two years of treatment, as well as in the age- and gender-matched general population (n = 1482) (* denotes a significant improvement from baseline at the $p < 0.05$ level; ** at the $p < 0.01$ level, and *** at the $p < 0.001$ level).

5.2.2 Costs

The mean cost of providing specialist treatment during the two-year follow-up was €20 621 (SD 23 167).

5.2.3 Cost-utility and sensitivity analysis in anorexia nervosa

The mean number of QALYs gained is presented in Study II, Table 1. In the best-case sensitivity analysis, the cost per QALY gained was €5296. Using discounted (3%) values for QALYs, the cost per QALY gained increased to €11 559. In the base-case analysis, the mean cost per QALY gained was €64 440. Using discounted (3%) values for QALYs, the cost per QALY gained increased to €71 600.

5.3 Bayesian prediction of the treatment outcome in anorexia nervosa (Study III)

The baseline characteristics of anorexia nervosa patients are presented in Table 6. The results of four outcome variables are presented in Study III, Table 1. The sum variable was correlated with the EDI variable (Pearson correlation coefficient 0.74) and the BMI variable (Pearson correlation coefficient 0.48). No other correlation was statistically significant.

In NBC analysis, the sum of the outcome variables and EDI could not be predicted from this data set. A simple model with three predictor variables was found for HRQoL. A lower HRQoL after two years of treatment was predicted by a lower score in the vitality dimension at baseline (15D), more strongly controlled eating from the questionnaire designed for this study and a poor self-reported baseline health status.

For the BMI outcome variable, a model with two predictor variables was found. A lower baseline BMI and lower score in the 15D eating dimension (indicating further need for help with eating) predicted in the two-year follow-up a BMI value of less than 19 kg/m^2. These models are presented in Study III, Figures 1 and 2.

A fixation table of the model predicting the outcome variable QoL is presented in Study III, Table 3. The model was fixed to different values to demonstrate the effect of fixation on the target variable. A corresponding fixation table for the target variable BMI is presented in Study III, Table 4.

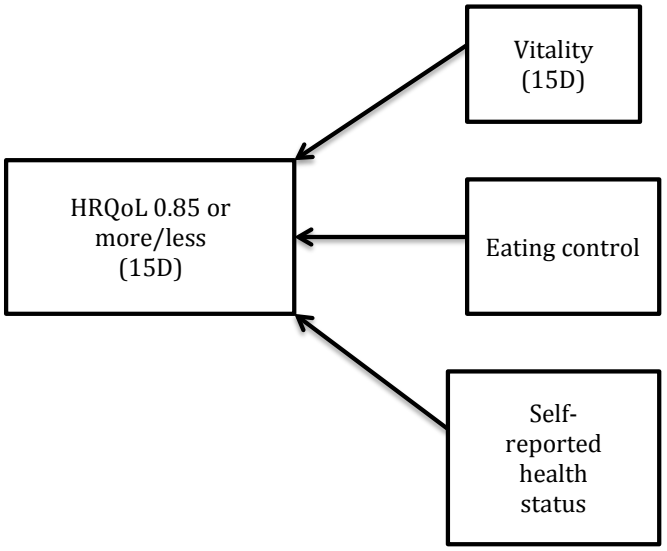


Figure 8. A naïve Bayesian classifier (NBC) model for predicting the outcome variable HRQoL.

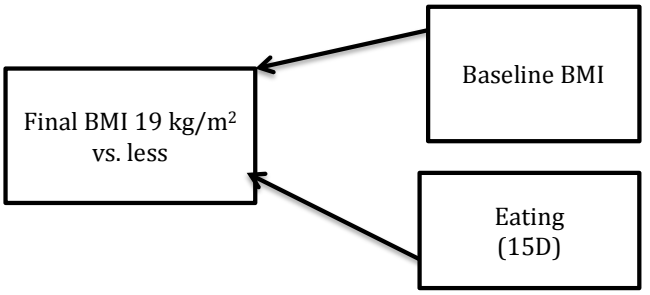


Figure 9. A naïve Bayesian classifier (NBC) model for predicting of outcome variable BMI.

5.4 Long-term health-related quality of life in eating disorders (Study IV)

5.4.1 Clinical outcomes

5.4.1.1 Anorexia nervosa

Anorexia nervosa (n = 47) patient characteristics (with SDs) are presented in **Table 7**. The values are means (and SD) or percentages. (AN = anorexia nervosa, HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index)

Table 7. Baseline characteristics of the anorexia nervosa patients. Values are means (and SD) or percentages. (HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index).

Variable	Anorexia Nervosa (n=47)
Mean Age, years (SD) (Age range)	23(7.8) (17-64)
Female %	100
HRQoL-score	0.807 (0.123)
EDI –score	74 (29)
BMI kg/m2	16.4 (2.1)

Compared with the mean 15D score of the age-matched general female population, AN patients had a global, severe deterioration in their HRQoL. During the follow-up there was a significant improvement in seven dimensions and in the mean 15D score (Figure 3). There was also a significant improvement in the EDI and BMI (Table 2). Although improvement occurred in

the HRQoL, it still remained severely impaired compared to the general population (0.893 vs. 0.935, $p < 0.001$). The average BMI of AN patients reached a normal level (20.1), since the cut-off for being underweight is normally considered as BMI > 18.5 (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html].

Table 8. Baseline characteristics and follow-up outcomes in anorexia nervosa. Values are means (and SD) or percentages. (HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index).

Variable	Anorexia nervosa (n = 47)	Significance of change compared to baseline (p-value)
HRQoL at baseline	0.807 (0.123)	
HRQoL at 8 years	0.893 (0.079)	< 0.001
EDI at baseline	74 (29)	
EDI at 8 years	44(28)	< 0.001
BMI at baseline	16,4(2.1)	
BMI at 8 years	20.1 (2.8)	< 0.001

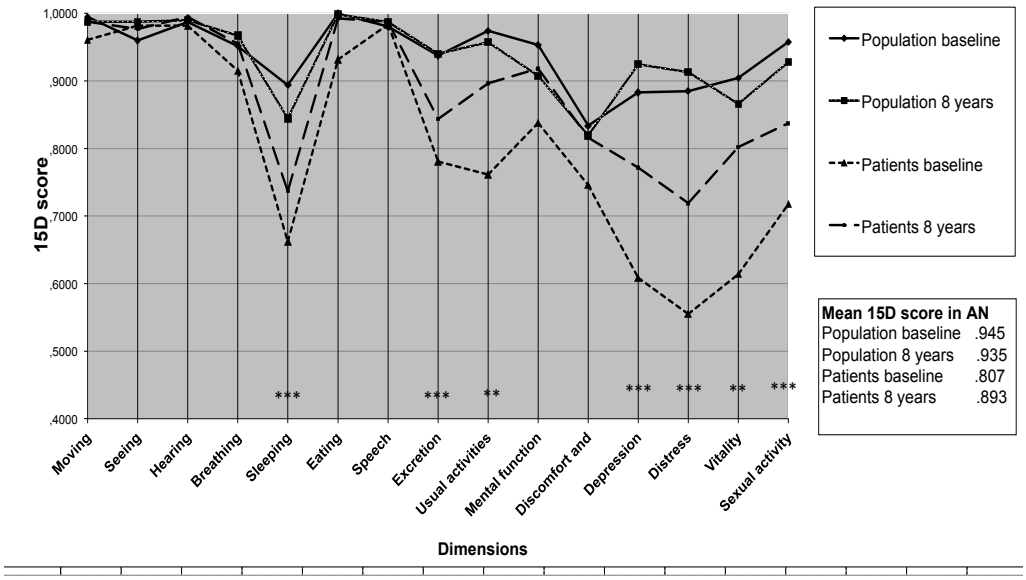


Figure 10. The 15D profiles of anorexia nervosa (AN) patients (n = 47) at baseline and after approximately 8 years of treatment, as well as in the age- and gender-matched general population at baseline and after 8 years (n = 2342) (* denotes a significant improvement from baseline at the $p < 0.05$ level; ** at the $p < 0.01$ level, and *** at the $p < 0.001$ level).

5.4.1.2 Bulimia nervosa

The baseline patient characteristics of the BN patients are presented in **Table 9.**

Table 9. Baseline characteristics of the bulimia nervosa patients. Values are means (and SD) or percentages. (HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index).

Variable	Bulimia Nervosa (n=54)
Mean Age, years(SD) (Age range)	25.7(6.0) (17-45)
Female %	100
HRQoL-score	0.818 (0.088)
EDI –score	82 (32)
BMI kg/m2	21(7.3)

The HRQoL of BN patients was significantly diminished compared to the age-matched general female population. There was a statistically significant improvement in the mean score and nine subscales of 15D during the follow-up (Figure 4). The EDI score improved significantly, but there was no change in BMI during the follow-up. In BN, the HRQoL also remained severely impaired compared to the general population (0.885 vs. 0.938, $p < 0.001$) (**Table 10**).

Table 10. Baseline characteristics and follow-up outcomes in bulimia nervosa. Values are means (and SD) or percentages. (HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index).

Variable	Bulimia Nervosa (n=54)	Significance of change compared to baseline (p-value)
HRQoL at baseline	0.818 (0.088)	
HRQoL at 8 years	0.885 (0.093)	< 0.001
EDI at baseline	82 (32)	
EDI at 8 years	44 (32)	< 0.001
BMI at baseline	21(7,3)	
BMI at 8 years	23(5,3)	NS

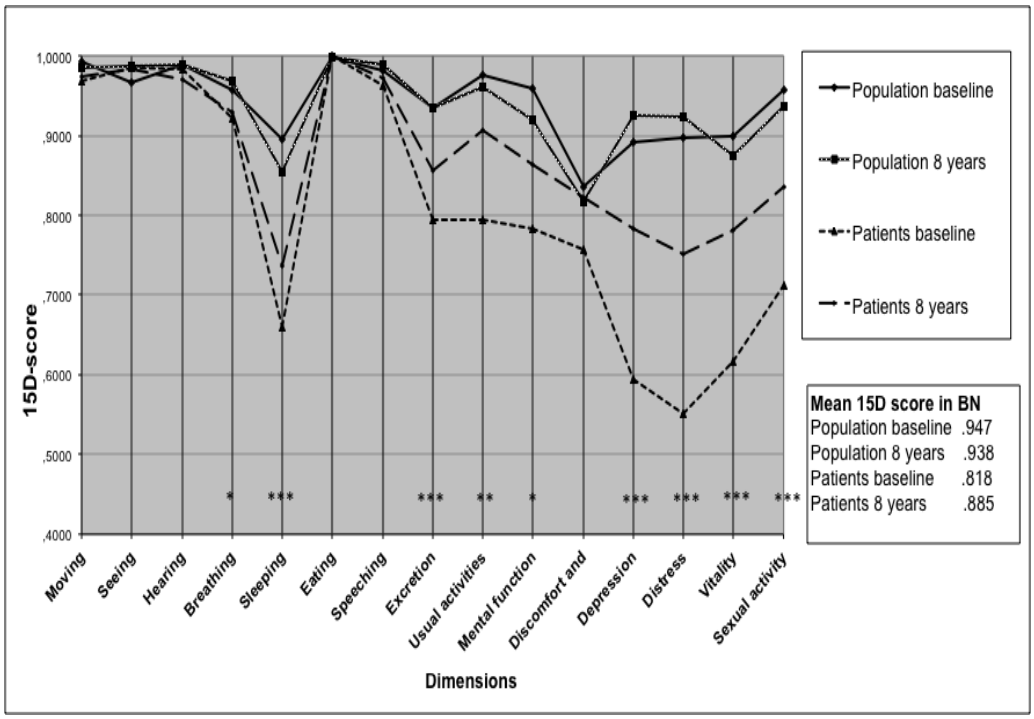


Figure 11. The 15D profiles of bulimia nervosa (BN) patients (n = 54) at baseline and after approximately 8 years of treatment, as well as in the age- and gender-matched general population at baseline and after 8 years (n = 1215) (* denotes a significant improvement from baseline at the $p < 0.05$ level; ** at the $p < 0.01$ level and *** at the $p < 0.001$ level).

6 DISCUSSION

6.1 Main findings

In this naturalistic follow-up study of eating disorder patients, it was found that the HRQoL of female AN and BN patients is poor when entering treatment at the Eating Disorder Unit compared to the normal population. During the follow-up, the HRQoL of AN and BN patients improved significantly, but after 8 years it was still less than in the general population. However, at 8 years, the average BMI was normal and EDI scores indicated improvement in the psychological characteristics of EDs, but the HRQoL was still low. Prognostic factors concerning the HRQoL in AN were found to be a lower score in the vitality dimension at baseline (15D), more strongly controlled eating from the questionnaire designed for this study and a poor self-reported baseline health status.

Cost-effectiveness in terms of cost per QALY was measured in young women suffering from AN or BN. The cost per QALY in BN was less than the commonly cited guidelines recommend. In AN, the cost per QALY was in the same range as that of other cost per QALYs in somatic conditions treated at our hospital (e.g. hip arthroplasty, cataract surgery). The conclusions of our study can only be generalized to female AN and BN sufferers, since the participants of the study were all female. This is, however, usually the case in eating disorder studies.

6.2 Results in relation to previous studies

6.2.1 Cost-utility of bulimia nervosa and anorexia nervosa (Studies I and II)

6.2.1.1 HRQoL

In both BN and AN, the baseline HRQoL was worse than in the normal population, and a significant improvement in HRQoL was seen during the follow-up. However, the HRQoL of BN and AN remained compromised compared to the normal population. These findings are in line with previous studies, which have reported a global deterioration in the HRQoL of eating disorder patients (Padierna et al., 2000, 2002; Jenkins et al., 2011; Winkler et al., 2014; Abbate-

Daga et al., 2014) and a significant improvement in HRQoL after treatment (Padierna et al., 2002). Padierna (2000) investigated eating disorder outpatients (n = 197) as one group and found that the patients with eating disorders were more dysfunctional in all areas measured with the SF-36 compared with the general population. In a follow-up study of HRQoL, Padierna and colleagues measured HRQoL after 2 years from the start of treatment and found an improvement, but the HRQoL was still lower than in the general population.

In BN, the 15D score after treatment was 0.85, which is in the same range as in AN (0.86). This is in line with a recent meta-analysis finding no differences between diagnostic groups (Winkler et al., 2014). The profiles of the 15D dimensions in AN and BN were different. An AN-specific improvement was seen in the dimensions eating, usual activities and mental health. To our knowledge, no previous studies have measured the HRQoL of ED patients using the 15D. Thus, we are unable to compare our results to previous HRQoL ED studies using the 15D. However, compared to other psychiatric conditions, the HRQoL of AN (0.79) and BN (0.80) patients before treatment was higher than that seen in patients entering secondary care psychiatric treatment because of depression (0.698) (Suominen et al., 2011). Compared to the mean baseline HRQoL of patients entering secondary care treatment for a variety of somatic conditions, it was, however, much worse (Suominen et al., 2011).

The baseline HRQoL of BN and AN patients was in the same range as seen in much older patients suffering from chronic conditions such as stroke, macular degeneration or coronary heart disease in a population-based study using the 15D (Saarni et al., 2006). In a study by Keilen et al. (1994), it was also found in a group of women referred to a tertiary ED service that those with EDs reported a lower QoL than physically impaired (angina, cystic fibrosis) patients. Compared to other psychiatric conditions, AN and BN patients at baseline in our study had an even worse HRQoL than older (45–49 years) patients suffering from depression (0.84), alcohol dependence (0.89) or panic disorder (0.86) (Saarni et al., 2007). The HRQoL of BN and AN patients was in the same range as that of people suffering from anxiety disorders (0.832), agoraphobia (0.781), generalized anxiety disorder (GAD) (0.783) or dysthymia (0.766) (Saarni et al., 2007).

The mean improvement in the 15D score seen in eating disorder patients (0.063) was somewhat greater than that seen as a consequence of treatment for depression (0.051) or back surgery (0.047), and more than threefold greater than in patients who had undergone a hysterectomy (0.020) or cataract surgery (0.008) (Suominen et al., 2011).

6.2.1.2 Costs and cost-utility

In our study, the average cost of the treatment in BN was €3972 (SD 5518) and in AN €20 621 (SD 23 167), and the cost per QALY in AN was also higher than in BN. Other studies have demonstrated that the treatment of AN is most costly due to the fact that AN patients are often hospitalized. In a systematic review (Agh et al., 2016), the annual healthcare costs for AN varied considerably from €2900 to €55 270 and in BN from €888 to €18,823. The cost estimates varied considerably. However, several differences in the design and analysis of the costs in the studies reduce the comparability of the cost data.

Compared to some other interventions so far studied in our project, the cost per QALY in BN in the best-case scenario (ca. €4428 discounted at 5%) was in the same range as that of lumbar spine surgery (€3700) (Räsänen et al., 2007) or cataract surgery in the best case (€7967 for patients whose both eyes were operated) (Räsänen et al., 2006b), and only approximately one-third of that observed for total hip arthroplasty (€12 340) (Räsänen et al., 2007) (5% discount rate). In AN, the cost per QALY in the best-case scenario (€11 559 discounted at 3%) was less than that observed for primary total knee arthroplasty (€18 890, 3% discount rate) (Räsänen et al., 2007), and in the same range as cataract surgery (€11 609, 3% discount rate) (Räsänen et al., 2006b) or total hip arthroplasty (€9906, 3% discount rate) (Räsänen et al., 2007). Although the economic burden and health service use in eating disorders is usually considered substantial (Mitchell et al., 2009), in our study the cost per QALY in BN and AN treatment was in the same range as in other conditions treated in our hospital district.

It is difficult to compare our results with other psychiatric interventions, because so few studies have reported the cost per QALY in psychiatry. To our knowledge, there have been no previous studies measuring the cost per QALY of treatment in EDs studied in a naturalistic setting. However, it is noteworthy that the commonly cited guidelines recommend the adoption of interventions that cost less than $20 000 to $100 000 per QALY (approximately €16 400 to €82 000) (Laupacis et al., 1992; Hirth et al., 2000; Neuman, 2005). The cost per QALY in BN was less than the guidelines recommend, and in AN the cost per QALY was in the range the commonly cited guidelines recommend for the adoption of health care interventions. This indicates that the treatment of AN and BN is cost-effective in terms of cost per QALY.

6.2.2 Prognostic factors in anorexia nervosa (Study III)

To our knowledge, the literature includes no studies using HRQoL instruments for assessing prognostic factors in EDs. In our study, we found that a low *eating* dimension score in the 15D was associated with not reaching a BMI of at least 19 kg/m^2 during the two-year follow-up. A lower score in the 15D dimension *vitality* at baseline was associated with an impaired mean 15D score (less than 0.85). We also found out that high *eating control* at baseline was associated with a low HRQoL score two years after the start of treatment.

AN is often associated with several health problems (Goldbloom and Kennedy, 1995, Westmoreland et al. 2016). In our study, we found that a poor self-reported health status at baseline was associated with an impaired follow-up HRQoL. However, we could not distinguish whether poor general health is a consequence of AN or precedes the onset of AN. The results regarding BMI in our study are partially consistent with previous studies. A low baseline BMI was a risk factor for not reaching a BMI level of at least 19 kg/m^2 during a follow-up of two years, which is in line with previous studies (Steinhausen 2008; Castro-Fornieles et al., 2007).

Against our assumptions, the improvement in BMI did not correlate with an improvement in HRQoL during the follow-up. This raises the question of what really indicates an improvement in AN. It has been suggested in the literature (Jenkins et al., 2011) that people suffering from AN can sometimes view aspects of the disorder as a positive part of themselves. This egosyntonicity may cause denial of their problems regarding AN and their seriousness. It might also be that in those with limited insight, a self-reported QoL may fail to capture the degree of impairment. In a study by Doll and collegues (2005), for example, AN patients reported better QoL, but they still had a higher rates of suicidal thoughts and parasuicidal actions than subjects with other diagnoses. However, in a study by Bamford and Sly (2010), lower BMI predicted lower EDQoL in a sample of adults suffering from ED. In the literature, there are studies demonstrating that QoL worsens as BMI departs from the normal range (Abraham et al., 2006; Adair et al., 2007).

6.2.3 Long-term quality of life in eating disorders (Study IV)

The aim of our study was to measure for the first time the long-term development of health-related quality of life in AN and BN. According to our studies, the HRQoL appears to improve in AN the longer the patients are followed. The HRQoL of AN patients was 0.855 after 2 years of

follow-up. There was a clinically important (>0.03) improvement in HRQoL in AN from 2 years to 8 years (0.855 vs. 0.893). In BN, the HRQoL was 0.85 after 6 months from the start of the treatment, and it improved clinically importantly to 0.885 during the 8-year follow-up. However, the HRQoL was still severely impaired in both AN and BN compared to the normal population (0.94). Both AN and BN severely affected the QoL for a long period of time.

In our study, the HRQoL of both AN and BN patients 8 years after the start of the treatment was still significantly lower than in the normal population. This raises the question of what recovery in eating disorders means. Although the average BMI in AN had reached a normal level and the EDI score had significantly improved, the HRQoL was still impaired. De la Rie and colleagues (2005) also suggested in their study that symptom remission in EDs alone is not a sufficient condition for improvement in the quality of life.

6.3 Strengths and limitations

6.3.1 Strengths

6.3.1.1 Subjects

The study participants were "real-life patients" entering the outpatient or inpatient Eating Disorder Unit. Because of the naturalistic setting of the study, we did not want to exclude any patients. This gave us the possibility to gain more information on the everyday-life effectiveness and cost-utility of the routine treatment. The patients could have had a long history of eating disorders, many comorbidities and prior treatment elsewhere. The representativeness of the present study group was tested in terms of age, HRQoL, BMI and EDI, and they did not differ from the individuals who did not respond to the follow-up.

6.3.1.2 Study design

The strengths of this study are the long follow-up (8 years) and the inclusion of actual patients, who received treatment according the normal hospital routine. This gave us a possibility to gain more information on the actual treatment and its effectiveness.

6.3.1.3 Cost-utility and cost per QALY

The topic of Studies I and II was new. A strength of this study is that, to our knowledge, we were the first to measure the cost-effectiveness of routine treatment for eating disorders in terms of quality-adjusted life years. This is also the recommendation stated in the literature (Pirragilia et al., 2004). Furthermore, the costs of the treatment were actual costs obtained from our patient administration system and not cost estimates.

6.3.2 Limitations

6.3.2.1 Subjects

A shortcoming of this study is the limited number of patients, since only approximately half of the patients responded to the follow-up, and there was data missing. However, the patients were approached before the treatment even started and many of the patients may have decided not to begin the treatment, since ED patients are usually very ambivalent about receiving treatment, and dropout rates from inpatient treatment for eating disorders are very high (Pham-Scottez et al., 2012). The number of BED and EDNOS patients was also too limited to include in the analysis. In addition, the study group only consisted of female participants, so the conclusions can only be generalized to female samples, but this is usually the case in eating disorder studies (Jenkins et al., 2011).

A further drawback in this study is that the subjects were not representative of all individuals with anorexia nervosa and bulimia nervosa, as they were drawn from a group of patients entering treatment in a special-level tertiary Eating Disorder Unit.

6.3.2.2 Study design

The lack of measurement of psychiatric comorbidities is a major limitation, since depression or anxiety can affect the QoL (Gonzalez-Pinto et al., 2004), and this may be a confounding factor. The lack of measurement of the socioeconomic status of the family is also a limitation, since

higher parental education has independently predicted a higher rate of EDs in females (Ahren et al., 2013). We only measured the HRQoL with a generic instrument (15D), although in the literature it is suggested that generic QoL instruments may not be sufficiently sensitive to record the unique features that might be important for each disorder. ED-specific measures are better able to precisely measure QoL in ED samples (Engel et al., 2009). However, at the start of the study, no ED-specific measures were available to use. One shortcoming is the lack of a control group, since our results were compared to the age-adjusted general population.

6.3.2.3 Diagnostic interview and self-reported scales

The diagnosis was made by psychiatric resident or consultant after meeting with the patient. The lack of a structured diagnostic interview can be seen as a limitation. Other baseline data were gathered by using self-reported scales, which may possess reliability and validity problems. Although ED patients normally self-report their weight very accurately (McGabe et al., 2001), this can still cause major uncertainties. Finally, an extreme lack of insight in some ED patients may result in problems in self-reporting HRQoL (Jenkins et al., 2011; Engel et al., 2009).

6.3.2.4 Cost-utility and cost per QALY

A shortcoming of this study is that our cost data covered only the costs of specialized medical care. This may introduce some bias, as general health care utilization by eating disorder patients is high (Simon et al., 2005; Mitchell et al., 2009). We did not include indirect costs (losses of productivity: sickness absence, reduced productivity, premature death), which are major costs when concerning EDs.

One limitation is that the QALY calculations were based on the assumption that the improvement in HRQoL is long-lasting, although the course of eating disorders can be recurrent and patients may need treatment again. However, this kind type of calculation of QALYs is the approach typically used. Furthermore, knowledge of the long-term development of HRQoL is scarce, and the prognosis of patients not receiving any treatment is unclear. We made two

assumptions based on the literature and our clinical expertise, but the calculations of best-case and base-case analyses are only models and not actual costs.

7 CONCLUSIONS AND FUTURE PERSPECTIVES

7.1 Summary of main conclusions

Eating disorders are serious mental disorders affecting young people, and especially women. They have a major effect on the HRQoL of ED patients for a long period of time. The literature suggest that in people with subclinical pathology, QoL may still be negatively affected (Doll et al., 2005). According to our report, full recovery in terms of the health-related quality of life was not achieved even after 8 years after the start of the treatment. It should be recognised that after symptom remission, former patients can still suffer from diminished HRQoL, and a follow-up of the quality of life should be considered. Cost-effectiveness in terms of cost per QALY was measured in BN and AN. The cost per QALY in BN was less than the commonly cited recommend guidelines. In AN, the cost per QALY was in the same range as that of other cost per QALYs in somatic conditions treated at our hospital. However, all the participants were female, so the conclusions can only be generalized to female samples, although this is usually the case in eating disorder studies.

AN and BN are very serious conditions with high morbidity and a long-lasting impact on the HRQoL, even after symptom remission. In conclusion, the treatment of AN and BN is cost-effective and worthwhile.

7.2 Other conclusions

Our findings emphasize the importance of measuring the everyday-life effectiveness of routine treatment interventions. The patient perspective using the HRQoL instrument can provide us valuable information on the well-being of the patient when taking into consideration the long-

lasting impact of the disorder on HRQoL. Implementation of the routine measurement of HRQoL in the treatment of EDs should be considered. The everyday-life effectiveness of different treatment options should be studied, for instance in day patient vs. inpatient treatment or different psychological treatment options.

7.3 Clinical implications

It is important to know how and which patients with AN will respond to treatment. For example, those with a good prognosis may respond to less intensive treatment, while those with a worse prognosis may need more intensive treatment, e.g. inpatient treatment. We also need more information on how to improve or target the treatment at those patients not responding to first-line treatments. Knowledge of outcome factors may suggest how to do this (NICE Guidelines 2004). According to our study, we should put extra effort into the treatment of those AN patients who at baseline control their eating very strongly, have an extremely low BMI and report diminished vitality. We could have an impact on the prognosis of these patients by focusing on these clinical phenomena. This, however, should be examined in a future intervention study.

7.4 Implications for further research

Studies on the everyday-life effectiveness of treatment options should continue, since the results of randomized controlled trials (RCT) do not possibly reflect the situation of "real-life patients". A patient perspective should be included, e.g. by measuring the HRQoL using a generic and eating disorder a specific instrument. The follow-up should be long enough, since EDs are long-lasting and patients may have relapses. Cost-analysis should be incorporated into new studies, also measuring indirect costs. One should try to take into account the morbidity in eating disorders and the relapse rate, and thus create a model to estimate the actual cost per QALY. Comorbidities including depression and also the socio-economical status (SES) should be taken

into account in further studies on eating disorders and the health-related quality of life. More information on the cost per QALY in the treatment of EDNOS and BED is needed.

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REFERENCES

Aalberg V. Nuoruusiän psyykkinen kehitys. In Book Lastenpsykiatria ja Nuorisopsykiatria. Kirsti Kumpulainen, Eeva Aronen, Hanna Ebeling, Eila Laukkanen, Mauri Marttunen, Kaija Puura ja Andre Sourander. 2016.

Abbate-Daga G, Facchini F, Marzola E, Delsedime N, Giovannone C, Amianto F, Fassino S. Health-related Quality of Life in Adult Inpatients affected by Anorexia nervosa. Eur Eat Disord Rev 2014, 22, 285-291.

Abraham SF, Brown T, Boyd C, Luscombe G, Russell J. Quality of life: Eating disorders. Aust N Z J Psychiatry 2006 ;40(2):150-5.

Adair CE, Marcoux G, Ewashen C, Cram B, Ewashen CJ, Chafe J. Development and multi-site validation of a new condition-specific quality of life measure for eating disorders. Health Qual life Outcomes 2007; 5:23.

Adair CE, Marcoux GC, Bischoff TF, Cram BS, Ewashen CJ, Pinzon J, Gusella JL, Geller et al. Responsiveness of the eating disorders quality of life scale (EDQLS) in a longitudinal multi-site sample. Health Qual life Outcomes 2010;8:83.

Addington-Hall , Kalra L. Who should measure quality of life? BMJ 2001;322:1417-20.

Ackard DM, Richter S, Egan A, Engel S & Cronemeyer CL. Meaning of (Quality of) Life in Patients with Eating Disorders: A Comparison of Generic and Disease-Specific Measures Across Diagnosis and Outcome. Int J Eat Disord 2014; 47:259–267)

Agras WS. The consequences and costs of the eating disorders. Psychiatr Clin North Am 2001;24:371-386

Agh T, Kovacs G, Supina D, Pawaskar M, Herman BK, Voko Z, Sheehan DV. A systematic review of the health-related quality of life and economic burdens of anorexia nerosa, bulimia nervosa and binge eting disorder. Eat Weight Disord 2016; epub ahead of print.

Ahren JC, Chiesa F, Koupil I, et al. We are family- parents, siblings and eating disorders in a prospective total-population study of 250,000 Swedish males and females. Int J Eat Disord 2013;46:693-700.

Alanne S, Roine RP, Räsänen P, Vainiola T, Sintonen H. Estimating the minimum important change in the 15D scores. Qual Life Res 2015;24:599-606.

Andreas M, Baguley T. Prior approval: the groth of Bayesian methods in psychology. Br J Mathematical and Statistical Psych 2013;66-1-7.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington DC: American Psychiatric Publishing;1980.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington DC: American Psychiatric Publishing;1994.

American Psychiatric Association Practice guidelines for the treatment of patients with eating disorders. Practice guidelines for the treatment of psychiatric disorders (3rd ed) Arlington: American Psychiatric Association, 2006: 1097–222.

Arcelus J, Mitchell AJ, Wales J, Nielsen S**.** Mortality Rates in Patients with Anorexia Nervosa and other Eating Disorders. A Meta-analysis of 36 studies. Arch Gen Psychiatry 2011, 68, 724-731.

Arigo D, Anskis AM, Smyth JM. Psychiatric comorbidities in women with celiac disease. Chronic Illn, 2012;8: 45–55.

Aromaa A, Koskinen S. (eds). Health and Functional Capacity in Finland. Baseline Results of the Health 2000 Health Examination Survey. Helsinki: Publications of the National Public Health Institute B12, 2004

Ashby D. Bayesian statistics in medicine: a 25 year review. Stat Med 2006;25:3589-631.

Avena NM. Examining the addictive-like properties of binge eating using an animal model of sugar dependence. Exp Clin Psychopharmacol 2007; **15:** 481–91.

Baiano M, Salvo P, Righetti P, Cereser L, Baldissera, Camponogara, Balestieri M. Exploring health-related quality of life in eating disorders by a cross-sectional study and a comprehensive review. BMC Psychiatry 2014;14:165-

Bacaltchuk J and Hay P. Antidepressants versus placebo for people with bulimia nervosa. Cochrane Database of systematic reviews 2003.

Bamford B, Sly R. Exploring quality of Life in the Eating Disorders. European Eating Disorders Review 2010, 147-153.

Bayes T, Price R. An essay towards solving a problem in the doctrine of chances. By the late Rev. Mr. Bayes, F.R.S. Comminicated by Mr. Price, in a letter to John Canton, A.M.F.R.S. Philosophical Transactions, 53,370-418, 1763.

Becker AE, Burwell, Ra, Herzog DB, Hamburg P, Gilman SE. Eating behaviours and attitudes following prolonged exposure to teleision among ethnic Fijian adolescent girls. BR J Psychiatry 2002;180:509-514.

Bellazzi R, Zupan B. Predictive data mining in clinical medicine: current issues and guidelines. Int J Med Inform 2008;77:81-97.

Ben-Tovim DI, Walsker K, Gilchrist P, Freeman R, Kalucy R, Esterman A. Outcome in patients with eating disorders: a five-year study. The Lancet 2001;357;1254-1257.

Benini L, Todesco T, Dalle Grave R, Deiorio F, Salandini L, Vantini I. Gastric emptying in patients with restricting and binge/purging subtypes of anorexia nervosa. Am J Gastroenterol 2004;99:1448-1454.

Bennett K, Stevens R. The internal structure of eating disorder inventory. Health Care Women Int 1997;18:495-504.

Berkman ND, Lohr KN; Bulik CM. Outcomes of eating disorders: a systematic review of the literature. Int J Eat Disord 2007;40:293-309.

Berges JM, Wall M, Larson N, Eisenberg ME, Loth KA, Neumark-Sztainer D. The unique and additive associations of family functioning and parenting practices with disordered eating behaviors in diverse adolescents. J Behav Med. 2014;37:205–217

Brambilla F, Garcia CS, Fassino S, et al. Olanzapine therapy in anorexia nervosa: psychobiological effects. Int Clin Psychopharmacol 2007; **22:** 197–204.

Braun, D.L., Sunday, S.R. & Halmi, K.A. Psychiatric comorbidity in patients with eating disorders. Psychological Medicine 1994*, 24,* 859–867.

Bissada H, Tasca GA, Barber AM, Bradwejn J. Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2008; 165**:** 1281–88.

Bizeul, Sadowsky N, Rigaud D. The prognostic value of initial EDI scores in anorexia nervosa: a prospective follow-up study of 5-10 years. Eur Psychiatry 2001; 16(4);232-8.

Black N, Burke L, Forrest CB, Sieberer UH, Ahmed S, Valderas JM, Bartlett SJ. Patient-reported outcomes: pathways to better health, better services, and better societies**.** Qual Life Res 2016; ;25(5):1103-12.

Blinder BJ, Cumella EJ, Sanathara VA. Psychiatric comorbidities of female inpatients with eating disorders. Psychosom Med 2006;68:454-62

Blomstedt P, Soini EJ, Lahtinen J, Ryynänen O-P, Kuukasjärvi P, Corander J. Empirical evaluation of the predictive performance of classification tools in coronary heart disease – P-Course a Naive Bayes tool outperforms novel logistic regression approaches. ValueHealth 2007;10:428.

Boggiano MM, Artiga AI, Pritchett CE, Chandler-Laney PC, Smith ML, Eldridge AJ. High intake of palatable food predicts binge- eating independent of susceptibility to obesity: an animal model of lean *vs* obese binge-eating and obesity with and without binge- eating. Int J Obes 2007; 31**:** 1357–67.

Bogh EH, Rokkedal K, Valbak K. A 4-year follow-up on bulimia nervosa. Eur Eating Disord Rev 2005;13:48-53.

Bould H, Koupil I, Dalman C, et al. Parental mental illness and eating disorders in offspring. Int J Eat Disord 2015;48:383-391.

Bowling A.The effects of illness on quality of life: findings from a survey of households in Great Britain. J Epidemiol Community Health 1996; 50(2): 149-55.

Brown TA, Holland LA, Keel PK. Comparing operational definitions of DSM-5 anorexia nervosa for research context. Int J Eat Disord 2014;47:76-84.

Bulik CM, Klump KL, Thornton L, Kaplan AS, Devlin B, Fichter MM, Halmi KA, et al. Alcohol use disorder comorbidity in eating disorders: a multicenter study. J Clin Psychiatry 2004a; Jul;65(7):1000-6.

Bulik CM, Slof-Op't Landt MC, van Furth EF, Sullivan PF. The genetics of anorexia nervosa. Ann Rev Nutr 2007; 27: 263–75.

Bulik CM, Tozzi F. The genetics of bulimia nervosa. Drugs Today (Barc) 2004; 40: 741–49.

Bulik CM, Kleiman SC, Yilmaz Z. GEnetic epidemiology of eating disorders. Curr Opin Psychiatry 2016;29:383-388.

Byford S, Barrett B, Roberts C, et al. Economic evaluation of a randomised controlled trial for anorexia nervosa in adolescents. Br J Psychiatry 2007; 191: 436–40.

Calati R, De Ronchi D, Bellini M, Serretti A. The 5-HTTLPR polymorphisms and eating disorders: a meta-analysis. Int J Eat Disord 2011;44:191-199.

Cnattingius S, Hultman CM, Dahl M, Sparen P. Very preterm birth, birth trauma, and the risk of anorexia nervosa among girls. Arch Gen Psychiatry 1999;56:634–638.

Castro-Fornieles J, Casulà V, Saura B, Martínez E, Lazaro L, Vila M, Plana MT, Toro J. Predictors of weight maintenance after hospital discharge in adolescent anorexia nervosa. Int J Eat Disord 2007;40:129-3.

Castro-Fornieles J, Bargallo N, Lazaro L, et al. A cross-sectional and follow-up voxel-based morphometric MRI study in adolescent anorexia nervosa. J Psychiatr Res 2009; 43: 331–40.

Chesney E, ,Goodwin GM, Fazel S. . Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 2014; 12:153-160.

Clausen L. Time to remission for eating disorder patients: a 2 ½ year follow-up study of outcome and predictors. Nord J Psychiatry 2008;62:151-159.

Cooper PJ, Steere JA. Comparison of two psychological treatments for bulimia nervosa: implications for models of maintenance. Behaviour Research and Therapy 1995;33:875-885.

Coleman H, Altini M, Nayler S, Richards A. Sialadenosis: a presenting sign in bulimia. Head Neck 1998;20:758-762.

Christie D, Viner R. Adolescent development. BMJ 2005;330:301-304.

Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 2013;381:1371-1379.

Crow SJ, Nyman J. the cost-effectiveness of anorexia nervosa treatment. Int J Eat Disord 2004;35:155-160.

Crow SJ, Peterson CB. The economic and social burden of eating disorders. Evidence and experience in Psychiatry, ed M. Maj e. Al. Vol 6, 2003, Wiley: New York.

Crow SJ, Peterson CB, Swanson SA, Raymond NC, Specker S, Eckert ED, Mitchell JE. Increased mortality in bulimia nervosa and other eating disorders. Am J Psychiatry 2009a; 166 (12): 1342-6.

Crow SJ, Mitchell JE, Crosby RD, Swanson SA, Wonderlich S, Lancaster K. The cost effectiveness of cognitive behavioral therapy for bulimia nervosa delivered via telemedicine versus face-to-face. Behav REs Ther 2009;47:451-3.

Crow SJ, Agras WS, Halmi KA, Fairburn CG, Mitchell JE, Nyman JA. A cost effectiveness analysis of stepped care treatment for BN. Int J Eat Disord 2013;46(4):302-307.

Crow SJ. The economics of eating disorder treatment. Curr Psychiatry Rep 2014; 16(7):454.

Culbert KM, Racine SE, Klump KL. Research Review: What we have learned about the causes of eating disorders - a synthesis of sociocultural, psychological, and biological research. Journal of Child Psychology & Psychiatry & Allied Disciplines 2015; 56(11):1141-64,

Currin L, Schmidt U, Treasure J, Jick H. Time trends in eating disorder incidence. Br J Psychiatry 2005; 186**:** 132–35.

Centers for Disease Control and Prevention: measuring healthy days: population assessment of health-related quality of life. Atlanta, Georgia:CDCP;2000

De la Rie SM, Noordenbos G, van Furth EF. Quality of life and eating disorders. Quality of Life Research 2005;14(6):1511-1522.

Dellava JE, Thornton LM, Lichtenstein P, Pedersen NSL, Bulimk CM. Impact of broadening definitions of anorexia nervosa on sample characteristics J Psychiatr Res 2011;45:691-698.

Dessureault S, Coppola D, Weitzner M, Powers P, Karl RC. Barrett´s esophagus and squamous cell carcinoma in a patient with psychogenic vomiting. Int J Gastrointest Cancer 2002;32:57-61.

Dickerson JF, Debar L, Perrin NA, Lynch F, Wilson GT, Rosselli F. Health-service use in women with binge eating disorders. Int J Eat Disord 2010;44:524–530

Doll HA, Petersen SE, Stewart-Brown SL. Eating disorders and emotional and physical well-being: Associations between student self-reports of eating disorders and quality of life as measured by the SF-36. Qual Life Res 2005;14:705-717.

Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of 55 Health Care Programmes. Third edition. Oxford University Press 2005.

Editorial, Quality of life and clinical trials. Lancet 1995;345;1-2.

Eddy KT, Dorer DJ, Franko DL. Tahillani K, Thompson-Brenner H, Herzog DB. Diagnostic crossover in anorexia nervosa and bulimia nervosa: implications for DSM-VI. Am J Psychiatry 2008;165:245-250.

Eisler I, Simic M, Russell GF, Dare C. A randomised controlled treatment trial of two forms of family therapy in adolescent anorexia nervosa: a five-year follow-up. J Child Psychol Psychiatry 2007;48(6):552-60.

Engel SG, Wittrock DA, Crosby RD, Wonderlich SA, Mitchell JE and Kolotkin RL. Development and psychometric validation of an eating disorder-specific health-related quality of life instrument. Int J Eat Disord 2006;39:62-71.

Engel SG, Adair CE, Las Hayas C, Abraham S. Health-related quality of life and eating disorders: a review and update. Int J Eat Disord 2009;42:179-187.

Ehrlich S, Burghardt R, Weiss D, Salbach-Andrae H, Craciun EM, Goldhahn K et al. Glian and neuronal damage markers in patients with anorexia nervosa. J Neural Transm Vienna Austira 1996;115:921-927.

Faccini M, Sala L, Malfatto G, Bragato R, Redaelli G, Invitti C. Low-K+ dependent QT prolongation and risk for ventricular arrhythmia in anorexia nervosa. Int J Cardiol 2006;106:170-176.

Fairburn CG, Cooper Z, Doll H, Norman P, O'Connor M. The natural course of bulimia nervosa and binge eating disorder in young women. Arch Gen Psychiatry 2000; 57, 659–665.

Fairburn CG, Harrison PJ. Eating Disorders. Lancet 2003; 321:407-416.

Favaro A, Tenconi E, Santonastaso P. Perinatal factors and the risk of developing anorexia nervosa and bulimia nervosa. *Arch Gen Psychiatry* 2006; **63:** 82–88.

Favaro A, Tenconi E, Ceschin L, Zanetti T, Bosello R, Santonastaso P. In utero exposure to virus infections and the risk of developing anorexia nervosa. Psychol Med 2011a;41:2193–2199.

Favaro A, Tenconi E, Bosello R, Degortes D, Santonastaso P. Perinatal complications in unaffected sisters of anorexia nervosa patients: Testing a cova- riation model between genetic and environmental factors. Eur Arch Psychiatry Clin Neurosci 2011b;261:391–396.

Felce D, Perry J. Quality of life: its definition and measurement. Res Dev Disabil 1995; 16(1):51-74

Felce D. Defining and applying the concept of quality of life. J Intellect Disabil Res 1997; 41:126-35.

Fichter MM, Quadflieg N, Rief Q. Course of multi-impulsive bulimia. Psychol Med 1994;24:591-604.

Fichter MM, Quadflieg N. Twelve-year course and outcome of bulimia nervosa. Psychol Med 2004;34:1395-1406.

Fichter MM, Quadflieg N, Hedlund S. Twelve-year course and outcome predictors of anorexia nervosa. Int J Eat Disord 2006;39:87-100.

Fichter MM, Quadflieg N, Hedlund S. Long-term course of binge-eating disorder and bulimia nervosa: relevance for nosology and diagnostic criteria. Int J Eat Disord 2008;41:577-86.

Fichter MM, Quadflieg N. Mortality in Eating Disorders-results of a large prospective clinical longitudinal study. Int J Eat Disord 2016;49:391-401.

Foley DL, Craig JM, Morley R, Olsson CJ, Dwyer T, Smith K and Saffery R. Prospects for epigenetic epidemiology. Am J Epidemiol 2009; 169:389-400.

Fonseca H, Ireland M, Resnick MD. Familial correlates of extreme weight control behaviors among adolescents. Int J Eat Disord. 2002;32:441–448.

Frank GK, Bailer UF, Henry SE, et al. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [(11)C]raclopride. Biol Psychiatry 2005; 58**:** 908–12.

Gadalla T, Piran N. Co-occurrence of eating disorders and alcohol use disorders in women: a meta analysis. Arch Womens Ment Health 2007; 10: 133–40.

Gallagher MW, Brow TA. Bayesian Analysis of Current and Lifetime Comorbidity Rates of Mood and Anxiety Disorders In Individuals with Posttraumatic Stress Disorder. J Psychopathol Behav Assess 2015;37(1):60-66.

Garner DM, Olmsted MP, Polivy J. Development and validation of a multidimensional Eating Disorder Inventory for anorexia and bulimia. Int J Eat Disord 1983; 2, 15-34.

Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russel IT. The SF-36 Health Survey Questionnaire- an outcome measure suitable for routine use within the NHS? BMJ 1993;306:1140-1444.

Gill TM, Feinstein AR. A critical appraisal of the quality of quality of life measurements. Journal of the American Medical Association 1994; 272, 619–626.

Godart N, Radon L, Curt F, Duclos J, Perderaeu F, Lang F, Venisse JL, Halfon O, Bizouard P, Loas G, Corcos M, Jeammet P, Flament MF. Mood disorders in eating disorder patients: prevalence and chronoloy of ONSET. J Affect Disord 2015;185:115-122.

Goodman A, Heshmati A, Malki N, Koupil I. Associations between birth characteristics and eating disorders across the life course: Findings from 2 mil- lion males and females born in Sweden, 1975–1998. Am J Epidemiol 2014; 179:852–863.

Gorwood P, Kipman A, Foulon C. The human genetics of anorexia nervoa. European Journal of Pharmacology 2003;480-163-170.

Greenland S, Schwartzbaum JA, Finkle WD. Problems due to small samples and sparse data in conditional logistic regression analysis. Am J Epidemiol 2000;151:531-539.

Grenon R, Tasca GA, Cwinn E, Coyle D, Sumner A, Gick M, Bissada H. Depressive symptoms are associated with medication use and lower health-related quality of life in overweight women with binge eating disorder. Womens Health Issues 2010;20:435–440

Groleau P, Joober R, Israel M, Zeramdini N, DeGuzman R, Steiger H. Methylation of the dopamine D2 receptor gene promoter in women with a bulimia-spectrum disorde: associations with borderline personality disorder and exposure to childhood abuse. J Psych Res 2014;48:121-127.

Grilo CM, Pagano ME; Skodol AE, Sanislow CA, McGlashan TH, Gunderson JG, et al. Natural course of bulimia nervosa and of eating disorder not otherwise specified: 5-year prospective study of remissions, relapses, and the effects of personality disorder psychopathology. J Clin Psychiatry 2007;68:738-746.

Groesz LM, Levine MP, Murnen SK. The effect of experimental presentation of thin media images on body satisfaction: a meta- analytic review. *Int J Eat Disord* 2002; **31:** 1–16.

Goldbloom DS, Kennedy SH. Medical complications of anorexia nervosa. In Brownell KD, Fairburn CG (Eds.), Eating disorders and obesity: A comprehensive handbook. New York: Guilford, 1995.

Golden NH, Jacobson MS, Schebendach J, Solanto MV, Hertz SM, Shenker IR. Resumption of menses in anorexia nervosa. Arch Pediatri Adolesc Med 1997;151:16-21.

Gonzales-Pinto A, Inmaculada F, Cristina R, De Corres BF, Sonsoles E, Fernando R Purificacion L. Purging behaviors and comorbidity as predictive factors of quality of life in anorexia. Int J Eat Disord 2004;36:445-450.

Guyatt, G. H., Feeny, D. H. & Patrick, D. L. Measuring health-related quality of life. Annals of Internal Medicine 1993; 118, 622-629.

Gustafsson,A, Edlund B, Kjellin L, Norring C. Risk and protective factors for disturbed eating in adolescent girls - aspects of perfectionism and attitudes to eating and weight. Eur Eat Disord Rev. 2009 17(5):380-9

Haas L, Stargadt T, Schreyoegg J, Schlösser R, Danzer G, Klapp BF. Inpatient costs and predictors of costs in the psychosomatic treatment of anorexia nervosa. Int J Eat Disord 2012a; 45(2):214-21.

Haas L, Stargardt T, Schreyoegg J, Schlösser R, Hofmann T, Danzer G, Klapp BF. Introduction of DRG-based reimbursement in inpatient psychosomatics-an examination of cost homogeneity and cost predictors in the treatment of patients with eating disorders. J Psychosom Res 2012b;73:383-390.

Haines J, Kleinman KP, Rifas-Shiman SL, Field AE, Austin B. Examination of shared risk and protective factors for overweight and disordered eating among adolescents. Arch Pediatr Adolesc Med. 2010;164:336–343

Halmi KA, Eckert E, Marchi P ym. Comorbidity of psychiatric diagnoses in anorexia nervosa. Arch Gen Psychiatry 1991;48:712-8.

Hay P, Claudino A, Kaio M. Antidepressants versus psychological treatments and their combination for bulimia nervosa., Cochrane Database of Systematic Reviews, 2001.

Hay PJ, Bacaltchuk J. Bulimia nervosa. Clin Evid (Online) 2008; June 12, pii: 1009.

Hay P, Bacaltchuk J, Stefano S, Kashyap. Psychological treatments for bulimia nervosa and binging. Cohchrane Database of Systematic Reviews. 2009

Hay P. A systematic review of evidence for psychological treatments in eating disorders: 2005-2012. Int J Eat Disord 2013;46:462-69.

Hay P, Chinn D. Forbes D, et al. And the Royal Australian and New Zealand College of Psychiatrists. Royal Australian and New Zealand College of Psychiatrists clinical practise guidelines for the treatment of eating disorders. Aust N Z J Pscychiatry 2014;48:977-1008.

Hay PJ, Claudino AM, Touyz S, Elbaky GA. Individual psychological therapy in the outpatient treatment of adults with anorexia nervosa. Cochrane Database of Systematic Reviews, 2015.

Haynos AF, Pearxon CM, Utzinger LM, Wonderlich SA Crosby RD, Mitchell JE, et al. Effects of empirically derived personality subtyping on clinical symptoms and treatment response in bulimia nervosa. Submitted.

Hawthorne G, Richardson J, Day NA. A comparison of the Assessment of Quality of Life (AQoL) with four other generic utility instruments. Annals of Medicine 2001, 33, 358-370.

Hearing S. Refeeding syndrome. BMJ 2004;328:908-909.

Herpertz-Dahlman B, Seitz J, Konrad K. Aetiology of anoexia nervosa: from a "psychosomatic family model" to neuropsychiatric disorder? Eur Arch Psychiatry Clin Neurosci 2011;261:177-81.

Herpertz-Dahlman S, Schwarte R, Krei M, Egberts K, Warnke A, Wewetzer C, Pfeiffer E, Fleischhaker C, Scherag A, Holgkamp K, Hagenah U, Bühren K, Konrad K, Schmidt U, Schade-Brittinger C, Timmesfelc N, Dempfle A. Day-patient treatment after short inpatient care versus continued inpatient treatment in adolescents with anorexia nervosa (ANDI): a multicentre, randomised, open-label, non-inferiority treial. Lancet 2014;383:1222-1229.

Hirth RA, Chernen ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. Med Dec Making 2000,;20, 332-342

Higginson IJ, Carr AJ. Using quality of life measures in the clinical setting. BMJ 2001;322:1297-1300.

Hjern A, Lindberg L, Lindblad F. Outcome and prognostic factors for adolescent female in-patients with anorexia nervosa: 9- to 14-year follow-up. Br J Psychiatry 2006; 189: 428–32.

Hudson JI, Hiripi E, Pope HGjr Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007; 1;61(3):348-58.

Hunt SM, McKenna SP, McEwen, Williams J, Papp E. The Nothingham Health Profile: subjective health status and medical consultations. Soc Sci Med 1981;15:221-229.

Hutter G, Ganepola S, Hofmann WK. The hematology of anorexia nervosa. Int J Eat Disord 2009;42:293-300.

Ho PC, Dweik R, Cohen MC. Rapidly reversible cardiomyopathy associated with chronic ipecac ingestion. Clin Cardiol 1998;21:780-783.

Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. Curr opin Psychiatry 2006;19:389-394.

Isomaa R, Isomaa AL, Marttunen M, Kaltiala-Heino R, Björkqvist K. The prevalence, incidence and development of eating disorders in Finnish adolescents: a two-step 3-year follow-up study. Eur Eat Disord Rev 2009;17(3):199-207.

Jacobi C, Hayward C, de Zwaan M, Kraemer HC, Agras WS. Coming to terms with risk factors for eating disorders: application of risk terminology and suggestions for a general taxonomy. Psychol Bull 2004a; 130: 19–65.

Jacobi F, Wittchen HU, Holting C, Höfler M, Pfister H, Muller N, et al. Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health interview and examination Survey (GHS). Psychol Med 2004b;34:597-611.

Jennet B. Health technology assessment. The rule should be ”no evaluation- no technology”. BMJ 1992;305:67-8.

Jenkins PE, Hoste RR, Meyer C, Blissett JM. Eating disorders and quality of life: a review of the literature. Clinical Psychology Review 2011, 31,113-121.

Jacoangeli F, Masala S, Staar Mexxasalma F, Fiori R, Martinetti A, Ficoneri C, Novi B, Pierangeli S, Marchetti G, Simonetti G, Bollea MR. Amenorrhea after weight recovery in anorexia nervosa: role of body composition and endocrine abnormalities. Eat Weight Disord 2006;11:2026.

Johnson C, Wonderlich SA. Personality characteristics as a risk factor in the development of eating disorders. In JH Crowther Tennenmaum DL. (Eds), 1991:The of bulimia nervosa the individual and family context (pp 179-197)

Johnson JG, Cohen P, Kasen S, Brook JS. Childhood adversities associated with risk for eating disorders or weight problems during adolescence or early adulthood. Am J Psychiatry 2002;159:394-400.

Jones JM, Lawson ML, Daneman D, Olmsted MP, Rodin G. Eating disorders in adolescent females with and without type 1 diabetes: cross sectional study. BMJ 2000, 320: 1563–1566.

Joo JS, Ehrenpreis ED, Gonzalez L, et al. Alterations in colonic anatomy induced by chronic stimulant laxatives: the cathartic colon revisited. J Clin Gastroenterol 1998;26:283-286.

Kaye WH, Frank GK, Bailer UF, Henry SE, Meltzer CC, Price JD et al. Serotonin alterations in anorexia and bulimia nervosa: New insights from imaging studies. Physiol Behav 2005;85:73-81.

Kaye WH, Fudge JL, Paulus M. New insights into symptoms and neurocircuit function of anorexia nervosa. Nat Rev Neurosci 2009; 10**:** 573–84.

Keel PK, Mitchell JE. Outcome in bulimia nervosa. Am J Psychiatry 1997;154:313-321.

Keel PK, Mitchell JE, Miller KB, Davis TL, Crow SJ. Long-term outcome of bulimia nervosa. Arch Gen Psychiatry 1999,;56(1), 63–69.

Keel PK, Brown TA. Update on course and outcome in eating disorders. Int J Eat Disord 2010;43:195-204.

Keilen M, Treasure T, Schmidt U, Treasure J. Quality of life measurements in eating disorders, angina, and transplant candidates: are they comparable? Journal of the Royal Society of Medicine 1994; 87:441-444.

Keski-Rahkonen A, Hoek HW, Susser EX, Linna MS, Sihvola E, Raevuori A,, Bulik CM, Kaprio J, Rissanen A. Epidemiology and Course of Anorexia nervosa in the Community. Am J Psychiatry 2007;164, 1259-1265.

Keski-Rahkonen A, Hoek HW, Linna MS, Raevuori A, Sihvola E, Bulik CM, Rissanen A, Kaprio J. Incidence and outcomes of bulimia nervosa: a nationwide population-based study. Psychological Medicine 2009; 39: 823-831.

Keski-Rahkonen A., Raevuori A, Bulik CM, Hoek HW, Rissanen A, Kaprio J. Factors associated with recovery from anorexia nervosa: a population-based study. Int J Eat Disord 2014;47:117-123.

Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences and risk factors. Curr Opin Psychiatry 2016;29;340-345.

Keys A, Brozek J, Henschel A. The biology of human starvation. Minneapolis: University of Minnesota Press, 1950.

Klump KL, Bulik CM, Kaye WH, Treasure J, Tyson E. Academy for eating disorders position paper: eating disorders are serious mental illnesses. Int J Eat Disord 2009; 42**:** 97–103.

Koran LM, Agras WS, Rossiter EM, Arnow B, Schneider JA, TElch CF, Raeburn S, Brude B, Perl M, Kraemer HC. Comparing the cost effectiveness of psychiatric treatments: bulimia nervosa. Psychiatry Res 1995;8:13-21.

Krantz MJ, Sabel A, Sagar U, et al. Factors influencing QT prolongation in hospitalized patients with severe anorexia nervosa. Gen Hosp Psychiatry 2011;38:486-488.

Krauth C, Buser K, Vogel H. How high are the costs of eating disorders-anorexia nervosa and bulimia nervosa-for German society? Eur J Health Econ 2002;3:244-250.

Kruschke JK. Doing Bayesian data analysis. Burlington 2011, MA:Academic Press.

Lacey JH, Evans CD. The impulsivist: a multi-impulsive personality disorder. Br J Addict 1986;81:641-649.

Latner JD Vallance JK, Bucket G. Health-related quality of life in women with eating disorders: association with subjective and objective binge eating. J Clin Psychol Med Settings 2008;15:148-53.

Laupacis, A., Feeny, D., Detsky, A.S., & Tugwell, P.X. How attractive does a new technology have to be to warrant adoption and utilisation? Tentative guidelines for using clinical and economic evaluations. CAMJ 1992;146:473-481.

Las Hayas C, Quintana JM, Padierna A, Bilbao A, Munoz P, Madrazo A. The new questionnaire Health-related quality of life for eating disorders showed good validity ad reliability. J Clin Epidemiol 2006;59:192-200.

Lee M, Shafran R. Information processing biases in eating disorders. Clin Psychol Rev 2004; 24: 215–38.

Liyanage VRB, Jarmasz JS, Murugeshan N, Bigio MRD, Rategar M and Davie JR DNA modifications: Function and applications in normal and disease states. Biology 2014, 3:670-723.

Litmanen J, Fröjd S, Mattunen M, Isomaa R, Kaltiala-Heino R. Are eating disorders and their symptoms increasing in prevalence among adolescent population. Nord J Psychiatry 2016;14:1-6.

Linna MS, Raevuori A, Haukka J, Suvisaari JM, Suokas JT, Gissler M. Reproductive health outcomes in eating disorders. Int J Eat Disord 2013;46:826-33.

Lock J , Le Grange D, Agras WS, Moye A, Bryson SQ, Jo B. Randomized clinical trial comparing family-based treatment with adolescent-focused individual therapy for adolescents with anorexia nervosa. Arch Gen Psychiatry 2010;67:1025-32.

Lock J. An update on evidence-based psychosocial treatments for eating disorders in children and adolexcents. J Clin Child Adolesc Pscychol 2015;44:707-721.

Lucas AR., Melton,LJ. III, Crowson CS, O'Fallon VM. Long-term fracture risk among women with anorexia nervosa: A population-based cohort study. Mayo Clin. Proc 1999; 74, 972–977.

Lynch FL, StriegelMoore RH, Dickerson JF, Perrin N, Debar L, Wilson GT et al. Cost-effectiveness of guided self-help treatment for recurrent binge-eating. J Consult Clin Psychol 2010;78:322-333.

Lähteenmäki S, Saarni S, Suokas J, Saarni S, Perälä J, Lönnqvist J, Suvisaari J. Prevalence and correlates of eating disorders among young adults in Finland. Nord J Psychiatry 2014;68:196-203.

Mainz V, Schulte-Ruther M, Fink GR. Herpertz-Dahlmann B, Konrad K. Structral brain abnormalities in adolescent anorexia nervosa before and after recovery and associated hormonal changes. Psychosom med 2012;74:574-582.

Malik M, Stratton J, Sweeney WB. Rectal prolapse associated with bulimia nervosa: report of seven cases. Dis Colon Rectum 1997;40:1382-1385.

Martin J, Padierna A, Aguirre U, Quintana JM, Hayas CL, Munoz P. Quality of life among caregivers of patients with eating disorders. Qual Life Res. 2011;20(9):1359-69.

Marzola E, Nasser J, Hashim S, Shih P, Kaye W. Nutritional rehabilitation in anorexia nervosa: review of the literature and implications for treatment. BMC Psychiatry 2013;13:290.

Mascolo M, Dee E, Townsend R, Brinton JT, Mehler PS. Severe gastric dilatation due to superior mesenteric artery syndrome in anorexia nervosa. Int J Eat Disord 2015;48:532-534.

McGabe RE, McFarlane T, Polivy J, Olmstedt MP, Eating disorders, dieting and the accuracy of self reported weight. Int J Eat Disord 2001;29(1):59-64.

McHugh MD. Readines for change and short-term outcomes of female adolescents in residential treatment for anorexia nervosa. Int J Eat Disord 2007;40:602-12.

McElroy SL, Kotwal R, Keck PE Jr. Comorbidity of eating disorders with bipolar disorder and treatment implications. Bipolar Disord 2006; 8: 686–95.

Miller KK, Grindspoon SK, Ciampa J, Hier J, Herzog D, Klibanski A. Medical findings in outpatients with anorexia nervosa. Arch Intern Med 2005;165:561-566.

Miller KK, Lee EE, Lawson EA, Misra M, Minihan J, Grinspoon SK, Gleysteen S, Mickely D, Herzog D, Klibanski A. Determinants of skeletal loss and recovery in anorexia nervosa. J Clin Endocrinol Metab 2006; 91:2931-2937.

Mitchell JE, Myers T, Drpwby R, O´Neill G, Carlisle J, Gerlach S. Health care utilization in patients with eating disorders. Int J Eat Disord 2009 Sep;42(6):571-4I.

Moock J, Kohlmann T. Comparing preference-based quality-of-life measures: Results from rehabilitation patients with musculoskeletal, cardiovascular or psychosomatic disorders. Quality of life Research 2008, 17, 485-495.

Mond JM, Hay PJ, Rodgers B, Owen C, Beumont PJ. Assessing quality of life in eating disorder patients. Qual Life Res 2005;14:171-8. 2005

Myllymäki P, Silander T, Tirri H, Uronen P. B-course: a web-based tool for Bayesian and causal data analysis. Int J Artif Intell 2002: 11:369-387. (http.//b-course.cs.helsinki.fi/obc/)

Muhlau M, Gaser C, Ilg R, Conrad B, Leibl C, Cebulla MH, et al. Gray matter decreases of the anterior cingulate cortex in anorexia nervosa. Am J Psychiatry 2007;164:1850-1857.

Munoz P, Quintana, Las Hayas C, Aguirre U, Padierna A, Gonzalez´Torres MA: Assessment of the impact of eating disorders on quality of life using the disease-specific, health-related quality of life for eatint disorders (HeRQoLED) questionnaire. Qual Life Res 2009;18:1137-1146.

Mustelin L, Raevuori A, Hoek HW, Kaprio J, Keski-Rahkonen A. Incidence and weight trajectories of binge eating disorder among young women in the community. Int J Eat Disord 2015;48:1106-1112.

Mustelin L, Silén Y, Raevuori A, Hoek HW, Kaprio J, Keski-Rahkonen A. The DSM-5 diagnostic criteria for anorexia nervosa may change its population prevalence and prognostic value. Journal of Psychiatric Research 2016;77:85-91.

Myers TC, Wonderlich SA, Crosby R, Mitchell JE, Steffen KJ, SMyth J, et al. Is multi-impulsive buliia a distinct type of bulimia nervosa: Psychopathology and EMA findings. Int J Eat Disord 2006;39:655-661.

Mäkinen M. Psychological well-being and psychiatric disorders in 14- to 15 year-old Finnish scholl girls and boys with overweight and obesity, Doctoral Thesis, University of Helsinki, 2015.

Nagl M, Jacobi C, Pau M, Beesdo-Baum K, Hörler M, Lieb R, Wittchen H-U. Prevalence, incidence, and natural course of anorexia and bulimia nervosa among adolescents and young adults. Eur Child Adolesc Psychiatry 2016;25:903-918.

Neumann, P.J. Using cost-effectiveness analysis to improve health care: Opportunities and barriers. Oxford, England: Oxford University Press, 157-158, 2005.

Ng AY, Jordan MI. On discriminative vs. generative classifiers: a comparison of logistic regression and Naive Bayes, in: T. Dietterich, S. Becker, Z. Ghahramani (Eds.), Advances in Neural Information Processing Systems, vol. 14, MIT Press, Cambridge, 2002, pp. 605–610.

NICE guideline: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders. Clinical guidelines, Jan 2004.

Nomura Y, Wickramaratne PJ, Warner V, Mufson L and Weissman MM Family disorders, parental depression and psychopathology in offspring: Ten-year follw-up. J Am Acad Child Adolesc Psychiatry 2002; 41:402-409.

O´Brien JA, Patrick AR. The cost of acute hospitalization for Anorexia nervosa and Bulimia. Value Health 2001;2:148.

Oflaz S, Yucel B, Oz F, Sahin D, Ozturk N, Yaci O, Polat N, Gurdal A, Cizgici AY, Dursun M, Oflaz H. Assesment of myocardial damage by cardiac MRI in patients with anorexia nervosa. Int J Eat Disord 2013;46:862-866.

Ostlund H, Keller E, Hurd Y. Estrogen receptor gene expression in relation to neuropsychiatric disorders. Annals of the New York Academy of Sciences 2003; 1007:54-63

Orley J, Saxena S, Herman H. Quality of life an mental illness. Journal of Psychiatry 1998;172:291-293.

Padierna A, Quintana JM, Arostegui I, Gonzalez N, Horcajo MJ. The health-related quality of life in eating disorders. Quality of Life Research 2000, 9, 667-674.

Padierna A, Quintana JM, Arostegui I, Gonzalez N, Horcajo MJ. Changes in health related quality of life among patients treated for eating disorders. Qual Life Res 2002; 11:545-52.

Papadopolous FC, Ekbom A, Brandt L, Ekselius L. Excess mortality, causes of death and prognostic factors in anorexia nervosa. Br J Psychiatry 2009; 194: 10–17.

Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? Nature Rev Neurosci 2008;9:947–57.

Pham-Scottez A, Huas C, Perez-Diaz F, Nordon C, Divac S, Dardennes R, Speranza M, Rouillon F. Shy do people with eating disorders drop out from inpatient treatment? The role of personality factors. J Nerv Ment Dis 2012;200:807-13.

Pirraglia PA. Rosen AB, Hermann RC, Olchanski NV, Neumann, P. Cost utility analysis studies of depression management: a systematic review. Am J Psychiatry 2004; 161, 2155-2162.

Preti A, Girolamo Gd, Vilagut G, Alonso J, Graaf RD, Bruffaerts R, Demyttenaere K, Pinto-Meza A, Haro JM, Morosini P; ESEMeD-WMH Investigators. The epidemiology of eating disorders in six European countries: results of the ESEMeD-WMH project. J Psychiatr Res. 2009 ;43(14):1125-32.

Quadflieg N, Fichter MM .The course and outcome of bulimia nervosa. Eur Child Adol Psychi 2003;12:199-209.

Raevuori A, Hoek HW, Susser E ym. Epidemiology of anorexia nervosa in men: a nationwide study of Finnish twins. PLoS One 2009;4:e4402

Raevuori A, Linna MS, Keski-Rahkonen A. Prenatal and perinatal factors in eating disorders: a descriptive review. Int J Eat Disord 2014 Nov;47(7):676-85.

Raevuori A, Haukka J, Vaarala O, Suvisaari JM, Gissler M, Grainger M, Linna MS; Suokas JT. The increased risk for autoimmune diseases in patients with eating disorders Plos One 2014b Aug 22;9(8):e104845.

Raevuori A, Suokas J, Haukka J, Gissler M, Linna M, Grainger M, Suvisaari J. Highly increased risk of type 2 diabetes in patients with binge eating disorder and bulimia nervosa. Int J Eat Disord 2015 Sep;48(6):555-62

Revicki DA, Kleinman L, Cella D. A history of health-related quality of life outcomes in psychiatry. Dialogues Clin Nerosci 2014 Jun;16(2):127-35.

Rich LM, Caine MR, Findling JW, Shaker JL. Hypoglycemic come in anorexia nervosa. Case report and review of the literature. Arch Intern Med 1990;150:894-5.

Richter SK. Overview of normal adolescent development. In Handbook of child and adolescent psychiatry, Volume 6. Adolescence: development and syndromes. Edited by Noshpitz JD (editor-in-chief), Flaherty LT, Sarles RM. New York: John Wiley & Sons; 1998:15-25.

Rosenvinge JH, Martinussen M, Ostensen E. The comorbidity of eating disorders and personality disorders: A meta-analytic review of studies published between 1983 and 1998. Eat Weight Disord, 2000; 5:52-61

Royal College of Psychiatrists. Eating disorders in the UK: service distribution, service development and training, London 2012.

Russel G. Bulimia nervosa: an omious variant of anorexia nervosa. Psychol Med 1979;9:429-448.

Ruuska J. The Impact of Eating Disorders on the Adolescent Process. Thesis. Acta Universitatis Tamperensis; 1181, University of Tampere, Tampere 2006.

Ryynänen OP, Blomstedt P, Soini EJO, Lahtinen J , Kuukasjärvi P, Corander J. Improvement of predictions by multidimensional priors in P-course naïve Bayes classifier. Finnish Journal of eHealth and eWelfare. In press.

Räsänen P, Sintonen H, Ryynänen OP, Blom M, Semberg-Konttinen V. Roine RP. Measuring cost-effectiveness of secondary health care: feasibility and potential utilization of results. Int J Technol Assess Health Care 2005;21:22-31.

Räsänen P, Ohman J, Sintonen H, Ryynänen OP, Koivisto AM, Blom M, Roine RP. . Cost-utility of routine neurosurgical spinal surgery. J Neurosurg Spine 2006a;5:204–209.

Räsänen P, Krootila K, Sintonen H, Leivo T, Koivisto A-M, Ryynänen O-P, Blom M, Roine RP, Cost-utility of routine cataract surgery. Health Qual life Outcomes 2006b;4:74.

Räsänen P, Paavolainen P, Sintonen H, Koivisto A-M, Blom M, Ryynänen O-P, Roine RP. Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. Acta Orthopaedica 2007;78:108-115.

Saarni SI, Härkänen T, Sintonen H, Suvisaari J, Koskinen S, Aromaa A, Lönnqvist J. The impact of 29 chronic conditions on health-related quality of life: a general population survey in Finland using 15D and EQ-5D. Qual Life Res 2006;15:1403-14.

Saarni SI, Suvisaari J, Sintonen H, Pirkola S, Koskinen S, Aromaa A, Lönnqvist. Impact of psychiatric disorders on health-related quality of life: general population survey. Br J Psychiatry 2007;190 (4) :326-332.

Saarni SI, Viertiö S, Perälä J, Koskinen S, Lönnqvist J, Suvisaari J. Quality of life of people with schizophrenia, bipolar disorder and other psychotic disorders. Br J Psychiatry 2010;386-394.

Samara Mt , Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, Leucht S. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. JAMA Psychiatry 2016; 1;73(3):199-210.

Schmidt NB, Telch MJ. Prevalence of personality disorders among bulimics, nonbulimic binge eaters and normal controls. Journal of Psychopathology and Behavioral ass 1990; 12:169-185.

Schmidt U, Oldershaw A, Jichi F, et al. Out-patient psychological therapies for adults with anorexia nervosa: randomised controlled trial. Br J Psychiatry 2012;201:392-99.

Schmidt U. Aetiology of eating disorders in the 21 (st) century:new answers to old questions. Eur Child Adolesc Psychiatry 2013;12:130-137.

Schmidt U, Magill N, Renwick B, et al. The Maudsley Outpatient Study of Treatments for Anorexia nervosa and related conditions (MOSAIC): Comparison of the Maudsley model of Anorexia Nervosa Treamtn for adults

(MANTRA) with specialist supportive clinical management (SSCM) in outpatients with broadly defined anorexia nervosa: a randomized controlled trial. J Consult Clin Psychol 2015; 83:796-807.

Seitz J, Buhren K, von Polier GG, Heussen N, Herpertz-Dahlmann B, Konrad K. Morphological changes in the brain of acutely ill and weight recovered patients with anorexia nervosa. A meta-analysis and qualitative review. Z Kinder Jugendpsychiatr Psychoter 2014;42:7-17.

Seitz J, Walter M, Mainz V, Herpertz-Dahlman B, Konrad K, von Polier G. J Psychiatr REs 2015;68:228-37.

Shapiro JR, Berkman ND, Brownley KA, Sedway JA, Lohr KN, Bulik CM. Bulimia nervosa treatment: a systematic review of randomized controlled trials. Int J Eat Disord 2007; 40: 321–36.

Silen Y, Raevuori A, Juriloo E, Tainio VM, Marttunen M, Keski-Rahkonen A. Typical versus atypical anorexia nervosa among adolescents: clinical characteristics and implications for ICD-11. Eur Eat. Disord. Rev. J Eat. Disord Assoc. 2015;23:345-351.

Silverman JA. Richard Morton, 1637-1698. Limner of anorexia nervosa: his life and times. A tercentenary essay. JAMA 1983;250:2820-2.

Sintonen, H. The 15D-measure of health-related quality of life. I. Reliability, validity and sensitivity of its health state descriptive system. National Centre for Health Program Evaluation, Working Paper 41, Melbourne 1994a.

Sintonen, H. Outcome measurement in acid-related diseases. Pharmacoeconomics, 1994b; 5, 17-26.

Sintonen, H. The 15D-measure of health-related quality of life. II. Feasibility, reliability and validity of its valuation system. National Centre for Health Program Evaluation, Working Paper 42, Melbourne 1995.

Sintonen H. The instrument of health-related quality of life: properties and applications. Ann Med 2001;33:328-336.

Simon J, Schmitdt U,Pilling, S. The Health service use and cost of eating disorders. Psychological Medicine 2005;35:1543-51.

Sihvola E, Keski-Rahkonen A, Dick DM, Hoek HW, Raeuori A, Rose RJ, Pulkkinen L, Marttunen M, Kaprio J. Prospective associations of early-onset Axis I disorders with developing eating disorders. Compr psychiatry 2009;50(1):20-5.

Soini EJ, Rissanen T, Tiihonen J, Hodgins S, Eronen M, Ryynänen OP. Predicting forensic admission among the mentally ill in a multinational setting: A Bayesian modelling approach. Data KnowlEngin 2009;68:1427-40.

Skilton MR, Siitonen N, Wu€rtz P, Viikari JS, Juonala M, Seppala I, Laitinen T, Lehtimäki T, Taittonen L, Kähönen M, Celermajer DS, Raitakari PT. High birth weight is associated with obesity and increased carotid wall thickness in young adults: The cardiovascular risk in young Finns study. Arterioscler Thromb Vasc Biol 2014;34:1064–1068.

Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure quality of life, the doctor or the patient? Br J Cancer 1988; 57: 109-112.

Smink F, Hoeken van D, Hoek H. Epidemiology of eating disorders: incidence, prevalence and mortality rates. Curr Psychiatry Rep 2012; 14:406-4014

Smink FR, van Hoeken D, Hoek HW. Epidemiology, course, and outcome of eating disorders. Curr Opin Psychiatry.2013 Nov;26(6):543-8.

Smink FR, van Hoeken D, Oldehinkel AJ, Hoek HW. Prevalence and severity of DSM-5 eating disorders in a community cohort of adolescents. Int J Eat Disord 2014; 47(6):610-9.

Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health status predicts long- term outcome in outpatients with coronary disease. Circulation 2002;106:43–49.

Stavem, K. Reliability, validity and responsiveness of two multiattribute utility measures in patients with chronic obstructive pulmonary disease. Quality of Life Research 1999; 8: 45-54.

Steinhausen H-C. The outcome of anorexia nervosa in the 20th century. Am J Psychiatry 2002;159(8):1284-93.

Steinhausen HC, Grigoroiu-Serbanescu M, Boyadjieva S, Neumärker KJ, Winkler Metzke C. Course and predictors of rehospitalization in adolescent anorexia nervosa in a multisite study. Int J Eat Disord 2008;41:29-36.

Steinhausen HC, Weber S. The outcome of bulimia nervosa: finding from one-quarter century of research. Am J Psychiatry 2009;166:1331-1341.

Striegel-Moore R, Leslie D, Petrill SA, Garvin V, Rosenheck RA. One-year use and cost if inpatient and outpatient services among female and male patients with an eating disorder: Evidence from a national database of health insurance claims. Int J Eat Disord 2000; 27 :381-389.

Striegel-Moore RH, Franko DL. Epidemiology of binge eating disorder. Int J Eat Disord 2003;34:S19-S29.

Stuhldreher, N., Konnopka, A., Wild, B., Herzog, W., Zipfel, S, Löwe B, König H-H. Cost-of-illness studies and cost-effectiveness analyses in eating disorders: a systematic review. International journal of Eating Disorder 2012; 45:4:476-491.

Stuhldreher N, Wild B, Knig H-H, Konnopka A, Zipfel S, Herzog Q. Determinants of Direct and Indirect Costs in Anorexia Nervosa. Int J Eat Disord 2015;48:139-146.

Syömishäiriöiden käypä hoito suositus, 2014.

Suisman JL, o´Connor SM, Sperry S, Thompson JK, Keel PK, Burt SA, Klump KL. Genetic and environmental influences on thin-ideal internalixation. Int J Eat Disord 2012;54:942-948.

Suisman JL, Thompson JK, Keel PK, Burt SA, Neale M, Boker S, Klump KL. Genetic and environmental influences on thin-ideal internalixation across puberty and preadolescent, adolescent and young adult development. Int J Eat Disord 2014;47:773-783.

Suokas JT, Suvisaari JM, Gissler M, Löfman R, Linna MS, Raevuori AN, Haukka J. Mortality in eating disorders: a follow-up study of adult eating disorder patients treated in tertiary care, 1995-2010. Psychiatry Research 2013;210:1101-1106.

Suominen K, Karlsson H, Rissanen A, Valtonen HM, Räsänen P, Sintonen H, Roine RP. Perceived burden of illness in patients entering for treatment in a university hospital--is the threshold to secondary care higher for patients with depression than for those with somatic disorders? Eur Psychiatry 2011; 26(7):441-5.

Su X, Liang H, Yan W, Olsen J, Cnattingius S, Li J. Prenatal and early life stress and risk of eating disorders in adolescent girls and young women. Eur Child Adolesc Psychiatry 2016;25:1245-1253.

Swanson S, Crow S, Le Grange D, Swendsen J, Merikangas K. Prevalence and correlates of eating disorders in adolescents. Archives of General Psychiatry 2011;68:714-23.

Tchanturia, K., Morris, R., Surguladze, S. & Treasure, J. Perceptual and cognitive set shifting tasks in acute anorexia nervosa and following recovery. Eat. Weight. Disord_2002 ;Dec;7(4):312-5.

Tchanturia K, Davies H, Roberts M, Harrison A, Nakazato M, Schmidt U, Treasure J, Morris R. Poor c ognitive flexibility in eating disorders: examining the evidence using the wisconsin card sorting task. PloS one 2012;7;e28331.

Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Eng Med 1996;334:835-840.

Tiller J, Macrae A, Schmidt U, Bloom S, Treasure J. The prevalence of eating disorders in thyroid disease: a pilot study. J Psychosom Res 1994, 38: 609–616.

Titova OE, Hjorth OC, Schiöth HB, Brooks SJ. Anorexia nervosa is linked to reduced brain structure in reward and somatosensory regions: a meta-analysis of VBN studies. BMD Psychiatry 2013;13:110.

The WHOQOL Group: Development of the World Health Organization WHOQOL-BRIEF Quality of life assessment. Psycol Med 1998;28:551-558.

Thompson-Brenner H, Eddy KT, Franko DL, Dorer DJ, Vashchenko M, Kass AE, et al. A personality classification system for eating disorders: a longitudinal study. Compr Psychiatr 2008;49:551-560.

Thornton C, Russel J. Obsessive compulsive comorbidity in the dieting disorders. Int J Eat Disord 1997;21:83-87.

Treasure JL, Schmidt, U. Anorexia nervosa. Clin Evid 2002;8, 903–913.

Treasure JL, Claudino AM, Zucker N. Eating disorders**.** Lancet 2010; 375; 583-93

Toulany A, Wong M, Katzman DK, Akseer N, Steinegger C, Hancock-Howard RL, Coyte PC. Cost analysis of inpatient treatment of anorexia nervosa in adolescents: hospital and caregiver perspectives. CMAJ Open. 2015;2:E192-7.

Uhlen MM, Tveit AB, Stenhagen KR, Mulic A. Self-induced vomiting and dental-erosion- a clinical study. BMD Oral Health 2014;14:92.

Vainiola T, Penttilä V, Roine RP, Räsänen P, Rissanen AM, Sintonen H. Comparison of two utility instruments, the EQ-5D and the 15D, in the critical care setting. Intensive Care Med 2010*;* 36(12),:2090-3.

Vall, E ,Wade TD. Predictors of treatment outcome in individuals with eating disorders: a systematic review and meta-analysis Int J Eat disord 2015;48(7):946-71.

Van Hanswijck de Jonge P, Van Furth EF, Lacey JH, Waller G. The prevalence of DSM-IV personality pathology among individuals with bulimia nervosa, binge eating disorder and obesity. Psychol med 2003;33:1311-7.

Van den Eynde F, Treasure J. Neuroimaging in eating disorders and obesity: implications for research. Child Adolesc Psychiatr Clin N Am 2009; 18: 95–115.

Verbrugge LM, Jette AM. The disablement process Soc Sci Med. 1994; 38(1):1-14

Vincenzi B, O'Toole J, Lask B. PANDAS and anorexia nervosa: suggestions for medical assessment. Eur Eat Disord Rev 2010;18:116-23.

Westmoreland P, Krantz MJ, Mehler PS. Medical complications of Anorexia nervosa and Bulimia. The American Journal of Medicine 2016;129:30-37

Wade TD, Bergin JL, Tiggemann M, Bulik CM, Fairburn CG. Prevalence and long-term course of lifetime eating disorders in an adult australian twin cohort. Aust N Z Psychiatry 2006;40:121-8.

Wade TD, Gillespie N, Martin NG. A comparison of early family life events amongst monozygotic twin women with lifetime anorexia nervosa, bulimia nervosa, or major depression. Int J Eat Disord 2007; 40: 679–86.

Wade TD, Buik DM. Shared genetic and environmental risk factors between undue influence of body shape and weight on self-evaluation and dimensions of perfectionism. Psychol Med 2007;37:635-644.

Wade TD, Gordon S, Medland S, Bulik CM, Heath AC, Montgomery GW, martin NG. Genetic variants associated with disordered eating International journal of eating disorders 2013;46:594-608.

Walsh BT, Kaplan AS, Attia E, et al. Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. JAMA 2006; 295**:** 2605–12.

Wang D, Zhang W, Bakhai A. Comparison of Bayesian model averaging and stepwise methods for model selection in logistic regression. Stat Med 2004;23:3451-3467.

Wang LY, Nichols LP, Austin SB. The economic effect of Planet Health on preventing bulimia nervosa. Arch Pediatr Adolesc Med 2011;165:756-62.

Ware JE, Snow KK, Kosninski M, Reese PR. SF-36 Health Survey Manual and Interpretation Guide. Boston: Health Assessment Lab, New England Medical Center, 1993.

Welch, G., Hall, A., Norring, C. The factor structure of the Eating Disorder Inventory in patient setting. Int J Eat Disord 1990; 9: 79-85.

Wentz E, Lacey JH, Waller G, Rastam M, Turk J, Gillberg C. Childhood onset neuropsychiatric disorders in adult eating disorder patients. A pilot study. Eur Child Adolesc Psychiatry 2005; 14: 431–37.

Westerberg-Jacobson J, Edlund B, Ghaderi A. Risk and protective factors for disturbed eating: a 7-year longitudinal study of eating attitudes and psychological factors in adolescent girls and their parents. Eat Weight Disord 2010;15:e208-18

Whitney J, Murphy T, Landau S, et al. A practical comparison of two types of family intervention: an exploratory RCT of family day workshops and individual family work as a supplement to inpatient care for adults with anorexia nervosa. Eur Eat Disord Rev 2012;20:142-50.

Winkler, LA., Christiansen, E., Lichtenstein, MB., Hansenc NB, Bilenbergb N, Støvinga RK. Quality of life in eating disorders: A meta-analysis. Psychiatry Res. 2014,;219:1-9.

Wonderlich SA, Gordon KH, Mitchell JE, Crosby RD, Engel SG. The validity and clinical utility of binge eating disorder. Int J Eat Disord 2009;42:687-705.

Woodside DB, Garfinkel PE, Lin E, Goering P, Kaplan AS, Goldbloom DS, Kennedy SH. Comparisons of men with full or partial eating disorders, men without eating disorders, and women with eating disorders in the community. Am J Psychiatry 2001;158:570-574.

World Health Organization 2002, Global Programme on Evidence for Health Policy Discussion Paper No. 45 , The conceptual basis for measuring and reporting on health

Zipfel S, Löwe B, Reas DL, Deter HC, Herzog W. Long-term prognosis in anorexia nervosa: lessons from a 21-year follow-up study. Lancet 2000; 335: 721.

Zipfel S, Wild B, Gross G, et al. And the ANTOP study group. Focal psychodynamic threrapy, cognitive behaviour therapy and optimised treatment as usual in outpatients with anorexia nervosa (ANTOP study):randomised controlled tria. Lancet 2014;383:127-37.

Zipfel S, Giel KE, Bulik CM, Hay P, Schmidt U. Anorexia nervosa: aetiology, assessment, and treatment. The Lancet Psychiatry 2015;12:1099-1111.

Yao S, Kuja-Halkola R, Thornton LM, et al. Familial liability for eating disorders and suicide attempts: evidence fro a poplation registry in Sweden. JAMA Psychiatry 2016;73:284-291.

Ylimaz Z, Hardaway A, Bulik C. Genetics and epigenetics of eating disorders. Adv Genomics Genet 2015;5:131-150.

Xing JH, Soffer EE. Adverse effects of laxatives. Dis Colon Rectum 2001;44:1201-1209.

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